Archives of Neurology and Psychiatry

VOLUME 58 AUGUST 1947 NUMBER 2

VASOSPASM ASSOCIATED WITH MULTIPLE SCLEROSIS

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EIGHTEEN patients with multiple sclerosis were observed to show constrictions of some of the retinal arterioles. Scotomas were usually associated with the constrictions, and sometimes there was also a reduction in visual acuity. In most instances in which they were employed, fast-acting vasodilating drugs caused prompt, temporary reduction of the constrictions and of the size of the scotomas (sometimes to zero), and in several instances an increase of visual acuity as well.

When sufficiently frequent observations could be made, many of the constrictions proved to be transient, appearing and disappearing over a period and often shifting from one vessel to another. Scotomas frequently were transient, too, disappearing from one part of the visual field and reappearing in another. The constrictions were interpreted as spasms.[1]

PRELIMINARY OBSERVATIONS

CASE A.—The first case seen, that of a white man aged 30, was one of undiagnosed disease of the central nervous system. There was evidence of dissemination of lesions, but no definite diagnosis of multiple sclerosis or of any other condition could be made with assurance. In retrospect, multiple sclerosis may be the diagnosis. Nonetheless, this case became the starting point for the investigations to be reported, all the rest of which were made with patients who had ordinary, clinically indisputable multiple sclerosis.

Case A was studied in 1942 and 1943 by one of us (C. R. F.)[2] at the Neurological Institute of New York, in the service of Dr. Irving Pardee. Included in

This work was supported by the Fund for Research, Inc.

The ophthalmologic observations are Dr. Franklin's unless otherwise specified.

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Read at a meeting of the Inter-Hospital Conference of the New York State Department of Mental Hygiene, held at the New York Psychiatric Institute and Hospital, Sept. 11, 1946.

1. Brickner, R. M., and Franklin, C. R.: Visible Retinal Arteriolar Spasm Associated with Multiple Sclerosis: Preliminary Report, Arch. Neurol. & Psychiat. **51**:573 (June) 1944.

2. Franklin, C. R.: Presented at a meeting of the New York Academy of Medicine, Section of Ophthalmology in 1943.

the history were recurrent attacks of blindness of the left eye, lasting two to twenty-five minutes.

Fundi and Visual Fields.—On Jan. 15, 1943, while one of us (C. R. F.) was making rounds, the patient suddenly complained that his left eye was "closing." Ophthalmoscopic examination revealed the superior temporal artery to be a mere white streak. The venules in this region showed broken columns of blood, giving a box car appearance. This phenomenon lasted about three minutes, when the patient stated, "My eye has opened again and I can see." While the fundus was being observed, the arterioles gradually became pink; the color deepened progressively until the vessels appeared normal.

The vessels appeared normal in both eyes after the attack had passed. During the attack the left pupil measured about 5 mm. in diameter and did not react to light; the right pupil measured about 3 mm., and its reactions were normal. After the attack the pupils were of equal size, measuring about 3 mm.

At this time the papillas were objectively within normal limits, but later a comparative pallor of the temporal side of the left papilla was observed.

The visual fields, examined routinely on Dec. 22, 1942, had contained a rather large scotoma on the left when tested with 2 and 5 mm. test objects, while on the right a suggestion of contraction was found with a 2 mm. test object, both fields being taken at a distance of 1 meter. Reexamination on January 27 showed that the scotoma on the left had become greatly enlarged, and the right field showed a notch, homonymously placed.

For several years the patient continued to have similar attacks, always involving the left eye only. More recently slighter attacks have occurred in the right eye, according to the patient's reports. Attacks have sometimes been precipitated by either of two definite factors—sudden emotional tension or sudden exposure to bright light. For example, on one occasion the patient had been working in a tunnel for several hours; an attack occurred on his emerging into bright sunlight.

Case B.—F. M., a white woman aged 30, was referred by Dr. Bernard Glueck in February 1944. She presented a typical picture of multiple sclerosis, only moderately advanced.

Among her complaints were attacks in which the vision of the right eye became blurred and "shimmering." These attacks were particularly prone to occur during hot baths.

Fundi and Visual Fields.—F. M. was observed during and directly after several hot baths. In each instance she stated that she was undergoing an attack. At these times the retinal arterioles of the right eye regularly revealed constrictive changes.

On the first examination, Feb. 28, 1944, while the patient was complaining of a spontaneous attack (not following a bath), the pupil of the right eye was dilated with neo-synephrine hydrochloride (10 per cent). Pronounced constriction of all the ordinarily visible retinal arterioles was found. The arterioles were the size of threads, some of them being practically colorless. Many of these constrictions changed as the examiner watched; each of the four main divisions of the central retinal artery independently became dilated and constricted again. The changes were manifested by alterations in color and size. This gave the fundus a continuously shifting, kaleidoscopic appearance. The vessels of the fundus of the left eye were normal. In later examinations, after hot baths, the findings were less spectacular. Segmented constrictions were seen in various arterioles at different times.

The visual fields were plotted several times, using the right eye, immediately on the emergence of the patient from immersion for eight to ten minutes in water at a temperature of about 98 F. Multiple, small scotomas were found each time (fig. 1 *B*). The patient would state that she was experiencing an attack. In about ten minutes the attacks began to fade and the arterioles to return to their normal state. Visual fields plotted during the period of fading showed coalescence of some of the scotomas and disappearance of others.

Visual fields plotted between attacks showed only slight variation in number and position of scotomas in this case, and in no instance did the number of scotomas even approach what was found during attacks (fig. 1 *A*).

SYSTEMATIC OBSERVATIONS

Since these initial observations were made, 21 patients with multiple sclerosis have been studied systematically. The 21 patients have been divided into three groups: group A (13 patients), made up of those with scotomas; group B (4 patients), composed of those who could not cooperate well enough for satisfactory testing of the visual fields but

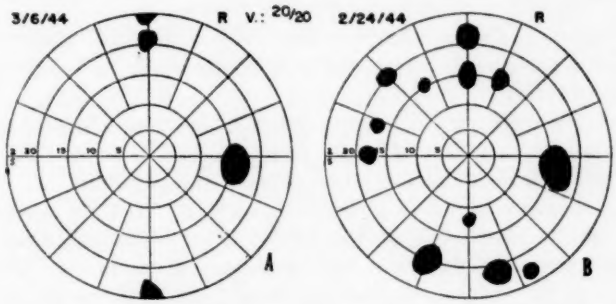

Fig. 1 (case B).—*A*, visual field in the right eye plotted between attacks with a 5 mm. test object at a distance of 1 meter. *B*, visual field in the right eye plotted immediately after the patient had been immersed in water at a temperature of about 98 F. for eight or ten minutes (5 mm. test object; distance 1 meter). The patient stated that she was experiencing an attack.

who had constrictions of retinal arterioles (these patients all had scotomas, although the latter could not be mapped out reliably), and group C (4 patients), comprised of those with no scotomas.

Experiments with vasodilating drugs were performed on 1 patient in group C and on 9 of the 13 patients in group A. (Of the 4 patients in group A not subjected to the drug tests, 1 (case 1) was incapacitated and could not come for the tests; 2 (cases 2 and 3) had no constrictions, and 1 (case 13) had scotomas which were too small to test. The last patient was subjected to another type of test however.

Most of the patients complained not only of dimness or blurring of vision, but of a "shimmering" (as in case B), which caused objects not only to shimmer but to be vaguer than normal in outline. Sometimes, in tests for visual fields the test object was said to "shimmer and fade."

TECHNIC OF EXAMINATION

Patients came to the office of one of us (C. R. F.), rested and then were subjected to an examination of the fundi and to plotting of the visual fields. (In cases A and B, all studies were performed at the Neurological Institute of New York.)

Examination of the Fundus.—Dilation of the pupils was not employed (except once in case B) because it might have altered the arteriolar conditions of the fundus and it was desired to avoid confusion of observations at this early stage of the studies.

Examination of the Visual Fields.—Fields were tested on a tangent screen with 2 and 5 mm. test objects, at a distance of 1 meter. Not more than two tests (before and after administration of drugs) were ever conducted in one day. Data on the visual fields of patients who could not cooperate adequately were not used; there were 4 such patients (group B), and only the observations on their fundi were incorporated in this report.

Determination of Visual Acuity.—Visual acuity was tested with correction when the acuity was less than 20/20. All reports of visual acuity in this paper include such corrections. Visual acuities were tested prior to the plotting of the fields, both before and after administration of drugs.

Administration of Drugs.—Amyl nitrite: Two or three whiffs were given. In no case were the general effects sufficiently disturbing to impair the patient's cooperation in the tests.

Papaverine Hydrochloride: A dose of 0.065 Gm. was administered by intravenous injection (in cases 7 and 9 the dose was 0.0325 Gm.). There were no general effects which impaired the cooperation of the patient.

Second Examination of Fundi and Visual Fields: After the administration of amyl nitrite the fundi were reexamined immediately. After the administration of papaverine hydrochloride the fundi were reexamined in two to three minutes. Reexamination of the visual fields was begun immediately after the second examination of the fundus.

THE FUNDI IN GROUP A (PATIENTS WITH SCOTOMAS)

The following types of arteriolar change were observed: A. Generalized narrowing of the whole arteriolar tree, with an arteriolar-venous ratio of less than 2 to 3. Generalized narrowing sometimes remained unchanged over a considerable period, but sometimes it varied; e. g., in case 12 it was less prominent than before in the left eye on June 29, 1944 (table 3).

B. Transient constriction of individual arterioles, in the presence of an otherwise normal arteriolar tree. Individual arterioles would be constricted at one observation and not at another. The constricted part of the vessel would appear much whiter than the rest. It would also be distinctly narrower than the adjoining parts of the vessel. The change was abrupt, both distally and proximally. Examples, seen in case 12, follow.

April 24, 1944 (during a "spontaneous" attack of impaired vision): Constriction of the right inferior temporal arteriole only was seen (generalized narrowing was present in this case, however).

May 26: No focal constrictions were observed on the right; constrictions of macular arterioles were seen on the left.

June 5: Constrictions of the right superior and inferior temporal arterioles and of the left macular arterioles were seen.

July 11: Constrictions of the right and left superior nasal arterioles only were observed.

Various Dates: Constrictions of the macular arterioles were seen on one or both sides.

Additional shifts, in this and in other cases, are recorded in table 3.

C. Alternating filling and emptying of an arteriole. This is an uncommon observation. It was seen in a left macular arteriole in case 6 on Sept. 19, 1944, and in case 17. The vessel would appear normal; suddenly it would become colorless, and then suddenly it would refill with blood. An identical phenomenon was seen in case 12 on June 16 (table 3, footnote). This alternation of events, which was repeated several times, occurred in rhythm with the pulse in cases 6 and 12, but it had its own slow, irregular rhythm in case 17. No evidence of glaucoma was found in either case.

D. Hourglass constriction. This was observed not uncommonly in one arteriole or another (table 3). The vessel was pinched and white at a given point and normal otherwise. Such constrictions were transient except in the right superior temporal arteriole in case 11; in this case an hourglass constriction was seen in the same place for over a year, although it was more prominent in the earlier observations than in the later ones. In addition, a fixed hourglass constriction was seen in the right superior nasal arteriole over a period of several months early in the same year; ultimately it disappeared. In case 7 an hourglass constriction of the superior nasal venule was observed twice.

E. Segmented constrictions. Broken columns of blood were seen in these vessels, with narrow, white areas between them. Distal to the constrictions the blood column was complete.

With all these types of constriction, the vessels were only rarely occluded completely. Blood could be seen in the vessel distal to the constriction. Complete closure was thought to have been observed only in cases A and B during the attacks.

The constrictions were seen usually in those parts of the vessels which lay on or near the papilla. There were exceptions (cases A, B and some others).

Some of the data suggested a tendency for the same vessel to be involved more than once, but the observations were not numerous enough to establish or negate the possibility finally. The most striking hint of it was the long-standing limitation of attacks to the left eye in case A, as stated previously.

Most commonly there was a frequent shifting of constrictions from one arteriole to another (table 3). An arteriole with a constriction on one day would be normal on another, and constrictions often were seen involving vessels which had been, and later were again, normal.

F. Pulsation of the whole arteriolar tree, independent of the constrictions, in rhythm with the pulse.

The arteriolar changes are recorded in full in table 3 and summarized in table 4.

It is unfortunate that, as a development of the war situation, we are unable to present photographs of the fundi. Dr. Sylvan Bloomfield, of the ophthalmologic service of the Mount Sinai Hospital, attempted to take pictures of transient constrictions (*B* of the classification). These were not in cases in which the constrictions were the most conspicuous, and the constrictions are not distinct enough in the photographs to warrant publication. Because of an unfortunate series of coincidences, facilities for photography were not available at times when hourglass, segmented or any conspicuous constrictions were seen. Paintings of some of the fundi were made by Mr. E. G. Bethke and Mr. Alfred Feinberg. Paintings prove nothing, but we are presenting one to illustrate segmented constrictions (*E* of classification; fig. 2).

SCOTOMAS

The scotomas sometimes showed considerable spontaneous variation in size and shift in position when the period of observation was prolonged. A scotoma present at one examination would be absent at the next, and a new one would be found in another position (figs. 1 and 3; table 3). This was noted often enough to warrant the suggestion that it may be characteristic of active multiple sclerosis. Often scotomas were multiple (figs. 1, 3, 4 and 5; table 3). Multiplicity of scotomas, like the other symptoms of the disease, is not rare in multiple sclerosis, although this was not appreciated until Lambert observed it.[3]

EFFECT OF DRUGS ON SCOTOMAS

Many scotomas were found to be reduced in size, or to be absent altogether, after the administration of amyl nitrite or of papaverine hydrochloride. Some scotomas, however, showed no change after administration of drugs.

Fixed and Transient Scotomas.—In case 12, during a period in which shifting and changing scotomas were recorded, a scotoma which remained fixed appeared on the left (fig. 3). It was a central scotoma, first detected as part of a larger, transient scotoma on May 26, 1944; it grew in size (June 5), merged with larger, transient scotomatous areas, was detectable again as an isolated scotoma on June 29, having become

3. Lambert, R. K.: Personal communication to the authors.

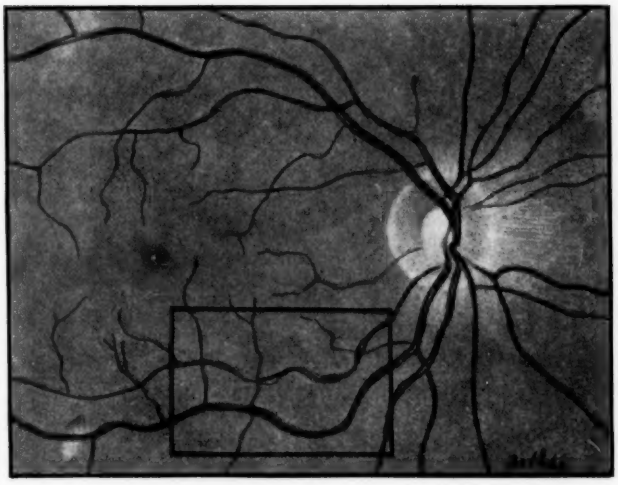

Fig. 2.—Retina in a case of multiple sclerosis in which the inferior temporal arteriole presents multiple segmented constrictions (*E* in classification in text) enclosed in the rectangle. In this picture, the constricted areas are shown as dark and the unconstricted ones as light. This is due to highlighting by the light reflex of the unconstricted areas during the artists's examination. More often the appearance was as described in the text, the constricted parts appearing lighter in color than elsewhere.

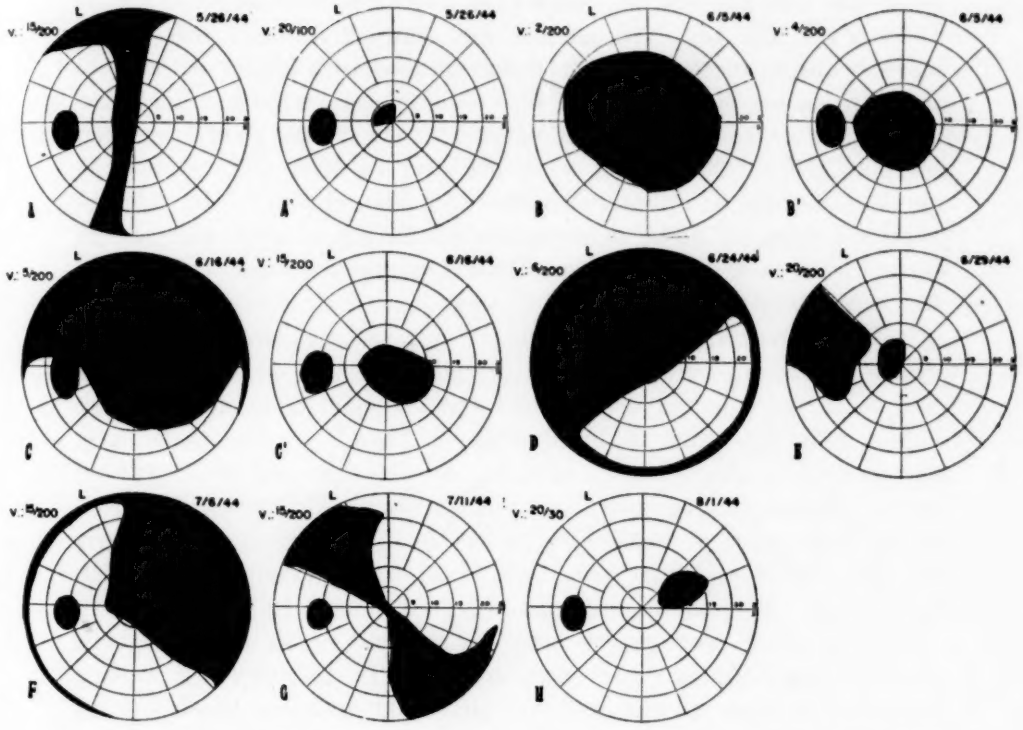

Fig. 3 (case 12).—Charts with plain letters represent a series of visual fields (left eye) plotted on various days. Charts with prime numbers show fields taken after administration of drugs, on the same day as the charts with the corresponding plain letters (e. g., *A*, on May 26, 1944, before injection of the drug, and *A'*, on May 26, after administration of the drug). The fields in successive observations can be followed independently of the drug experiments by ignoring the charts with prime numbers.

Papaverine hydrochloride was the drug used in all three of these experiments.

A 20 mm. test object was used at a distance of 1 meter except on May 26, when a 5 mm. test object was used.

The drug experiments (charts *A* and *A'*; *B* and *B'*; *C* and *C'*) show a striking reduction in the size of the scotoma following administration of the drug.

The sequential observations made on fields without drugs (charts *A, B, C, D, E, F, G and H*) show shifting of the position and change in size of the scotoma.

During a period when shifting and changing scotomas were recorded, a scotoma which remained fixed appeared on the left. It was a central scotoma, first detected as part of a larger, transient scotoma, on May 26; it grew in size (June 5), merged with larger, transient scotomatous areas, was detectable again as an isolated scotoma on June 29, having become reduced in size, and was last observed as part of another larger, transient scotoma on July 11. The identity and state of fixity of this central scotoma during the period when it was merged with larger scotomatous areas are shown by the effect of injections of papaverine hydrochloride. The larger areas, the transient nature of which was shown by their constant shifting of position and change in size, were caused by the drug to disappear, but the central scotoma remained. In fact, the central scotoma could be demonstrated as having its own independent existence at that time only by obliterating the transient scotomatous area with the drug.

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It might be conjectured that the central scotoma remained demonstrable because the drug was only partially effective and that a larger dose, or a more potent drug, might have caused its obliteration too. This is unlikely because of the constancy of the results, and particularly because on June 29 the central scotoma was demonstrated alone, without the preliminary employment of an injected drug. The patient had been taking large doses of papaverine hydrochloride by mouth, to be sure, but the same dosage had been maintained through July 6, on which date a larger scotomatous area had appeared, nonetheless.

Similar fixed scotomatous areas in company with transient ones were demonstrated in other cases as well. In case 6 there were a peripheral scotoma on the left and bilaterally enlarged blindspots on Sept. 19, 1944; only the peripheral scotoma was affected by amyl nitrite; on September 22 there was no peripheral scotoma but the blindspots were still enlarged, though smaller than on September 19. On September 28 the fields were normal (fig. 4). In case 9 there were a paracentral and two peripheral scotomas on the right on July 6, 7 and 8, 1944. The paracentral scotoma disappeared after the administration of drugs on July 7 and 8, while only one of the peripheral scotomas was affected. Reexamination on May 24, 1945 showed no paracentral scotoma; one peripheral scotoma was also gone (the one which had been affected by the drugs), while the other was smaller but was still represented vestigially. Case 5 provided an instance of an isolated, not very large, central scotoma, in which the center of the scotoma was fixed, while its peripheral part was transient and affected by the drugs. On June 23, 1944 the scotoma was reduced in size by amyl nitrite; on June 30 the scotoma was slightly smaller than it had been after administration of the amyl nitrite on June 23. Its peripheral, drug-affected part had disappeared, leaving the fixed core, which had been unaffected by the drug (fig. 5).

In addition, some scotomas were altogether unaffected by the drugs, as has been mentioned. In some instances (case 9, for example) in which a series of observations were made on serial days, one scotoma was persistently noted, and each time this was the one which remained

unaffected by the drugs. These phenomena are of interest in suggesting the existence of two distinct types of scotoma, the scotoma which is transient and affected by vasodilating drugs, and the scotoma which is fixed and unaffected by drugs.

EFFECTS OF ADMINISTRATION OF DRUGS ON BLOOD VESSELS

The inhalation of amyl nitrite almost uniformly produced general retinal vasodilatation. The constricted areas usually showed dilatation, but often it was less in degree than the rest of the vascular tree. In some instances the constriction disappeared altogether, whereas in others it was unaffected.

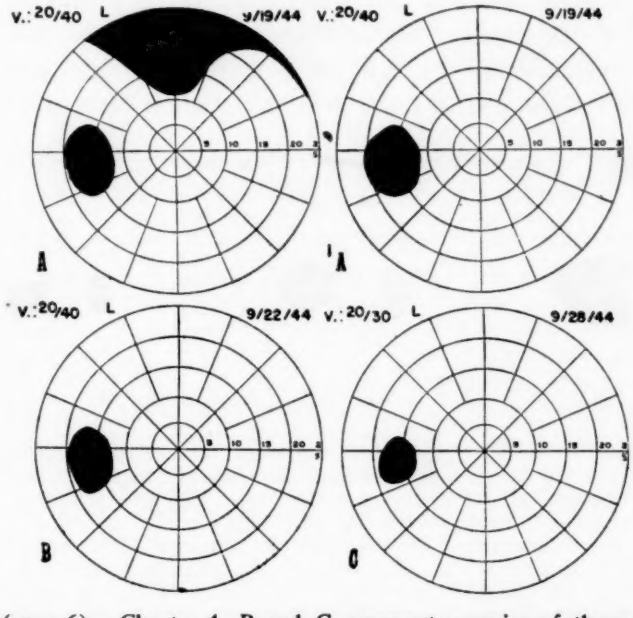


Fig. 4 (case 6).—Charts *A, B* and *C* represent a series of three visual fields (left eye) taken without drugs. Chart *A'* shows disappearance of the peripheral scotoma of chart *A* after administration of amyl nitrite, on Sept. 19, 1944.

The peripheral scotoma was not demonstrable on September 22 or 28. It is considered a transient scotoma, which can be affected by vasodilating drugs and which is the result of vasospasm without a fixed lesion. The enlarged blindspot, on the contrary, was not reduced in size by the amyl nitrite; if anything, it became slightly larger (paradoxic reaction of arterioles [?]; see text). In the subsequent observations, the size of the blindspot was found to be progressively smaller. The enlarged blindspot is considered a fixed lesion, the result of previous constrictions of greater intensity and/or longer duration than those responsible for the peripheral scotoma of September 19. The progressive reduction in size is not considered to be a consequence of vasodilatation but is thought to result from the healing processes of the tissue itself (5 mm. test object; distance, 1 meter).

The intravenous injections of papaverine hydrochloride sometimes appeared to produce general vasodilation also, and sometimes not. The vasodilation was less pronounced after papaverine hydrochloride than after amyl nitrite. The effect on constrictions, however, appeared quite similar to that of amyl nitrite.

The effects are summarized in terms of complete, partial or no relief of the constriction (table 3). In 18 trials with amyl nitrite, there were 4 instances of complete relief, 8 of partial relief and 7 of no effect. With papaverine hydrochloride, there were 4 instances of complete relief, 4 of partial relief and 7 of no effect.

A curious paradoxic effect was seen three times in case 11 and probably once in case 12. In case 11 the fixed hourglass constriction in the right superior temporal arteriole, instead of being reduced, extended distally along the vessel for a short distance after the inhalation of amyl nitrite (June 2 and 15, 1944). On earlier occasions, when this patient was in the Neurological Institute, similar effects on this constriction were observed after inhalation of amyl nitrite and after inhalation of carbon dioxide; at that time the patient had a similar hourglass constriction in the right superior nasal arteriole, seen regularly over a considerable period; and this constriction also extended along

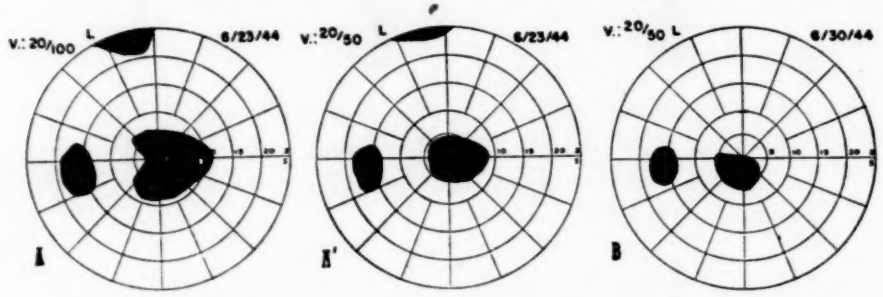


Fig. 5 (case 5).—Charts *A* and *B* represent two successive plottings of the visual field (left eye) on June 23 and 30, 1944, without drugs. *A'* shows reduction in size of the peripheral and central scotomas and a slight reduction of the slightly enlarged blindspot following administration of amyl nitrite, on June 23, 1944; the visual acuity also changed, from 20/100 to 20/50. On June 30 the peripheral scotoma was gone, and the central one was smaller; the slightly enlarged blindspot had become normal. Each of the three abnormalities is considered to represent a fixed lesion together with a transient disturbance, because each was partly unaffected and partly affected by the drug. It is considered that healing of tissues themselves occurred in the week between June 23 and June 30 in all three lesions—incomplete for the central scotoma and complete for the other two defects (5 mm. test object; distance, 1 meter).

the vessel after inhalations of the same substances. On June 2 the left macular arterioles, and on June 17 the left superior nasal arterioles, showed segmented constrictions after, but not before, the inhalation of amyl nitrite (not associated with changes in the visual fields; table 3, footnotes).

The probable paradoxic effect seen in case 12 occurred on May 26, when, after an injection of papaverine hydrochloride, a constriction which had not been present before appeared in the right inferior temporal arteriole. In this instance a peripheral scotoma at the top of the right visual field grew larger. Some doubt exists as to the

paradoxic nature of this observation, however, inasmuch as fifty minutes elapsed between injection of the drug and the second examination. In all other instances reexamination began within two or three minutes after administration of the drug. The fifty minute interval may have been sufficient for the new constriction to occur. (Despite this constriction, visual acuity improved slightly on the right [table 1]; it improved markedly on the left, where only a small central scotoma remained, no longer covering both sides of the point of fixation [fig. 3; table 1]).

EFFECT OF ORALLY ADMINISTERED MEDICAMENTS

No clearcut and indisputable effect on either scotomas or vascular constrictions was observed as a result of orally administered papaverine hydrochloride and other vasodilating drugs. The existence of spontaneous remissions in multiple sclerosis makes this problem difficult of approach in this manner.

EFFECT OF VARYING DOSES OF INTRAVENOUSLY ADMINISTERED PAPAVERINE HYDROCHLORIDE

As previously stated, the dose of papaverine hydrochloride employed in the experiments was 0.0325 or 0.065 Gm. The results were the same regardless of which dose was used. Differences might well be discovered in a larger series.

EFFECTS OF ADMINISTRATION OF DRUGS ON VISUAL ACUITY

Among the most striking observations were notable improvements in visual acuity immediately after the administration of the drugs in cases 5, 11 and 12. These changes are summarized in table 1 and further recorded in table 3.

The improvements in visual acuity in observations 1, 6, 7 and 8 coincide with reductions in size of central scotomas, or of large, bizarre scotomas which included central ones; in each of these instances the central part of the scotoma was included in the portion which became smaller after the administration of the drug (figs. 3 and 5). The improvement in observation 2 may perhaps be explained by the disappearance of the two small paracentral scotomas. In observation 4, many areas were involved in the spontaneous attack; those nearest the center had disappeared four hours later, when the second test was made. Observations 3 and 5 cannot be explained by the visual fields as recorded (table 3); they may possibly be accounted for by the disappearance of the shimmering vision, of which these patients, among others, complained.

In other cases no improvement in visual acuity followed administration of the drug.

CONSISTENCY AND INCONSISTENCY OF OBSERVATIONS ON THE VISUAL FIELDS AND FUNDI

In assessing the consistency of the positions of the constrictions with those of the scotomas, the following factors must be given attention: consistency in position before with that after administration of drugs; consistency in the course of repeated observations in a given case; consistency of visual acuity with scotomas and consistency of changes in one with those in the other after administration of drugs.

TABLE 1.—*Improvement in Visual Acuity Following Administration of Amyl Nitrite and Papaverine Hydrochloride*

				Visual Acuity				
				Before			Scotomas; Same Drug	
Observation	Case No.	Date	Eye	Amyl Nitrite	Papaverine	After Drug	Before	After
1	5	6/23/44	OS	20/100	.....	20/50	1 peripheral; 1 central	Both much smaller *
2	11	6/ 2/44	OD	20/40	.....	20/30	Enlarged blindspot; 2 paracentral; 3 peripheral	2 paracentral scotomas disappeared
3	..	6/15/44	OD	20/40	.....	20/30	Enlarged blindspot; 3 peripheral	1 peripheral scotoma disappeared
4	12	4/24/44	OS	20/40 (spontaneous attack)	.....	20/20 (spontaneous recovery)	See table 3	
5	..	5/26/44	OD	.....	20/30	20/20	1 peripheral	Enlarged blindspot †
6	..	.....	OS	.....	15/200	20/100	Bizarre, included central scotoma	Only small central scotoma remained
7	..	6/ 5/44	OS	.....	2/200	4/200	Large central scotoma	Grew smaller †
8	..	6/16/44	OS	.....	5/200	15/200	Bizarre, included central scotoma	Only smaller central scotoma remained †

* See figure 5.

† See figure 3. Note that on May 20 a fifty minute interval elapsed between the administration of papaverine hydrochloride and the second examination.

Consistency is not as simple to define as might be expected. A constriction in an inferior nasal arteriole is probably compatible with a scotoma in the superior temporal part of the field, or in the middle portion of the superior field if the constriction involves the main arteriole near its point of origin. However, if the constriction is in a small branch of a main vessel and the scotoma is a very large one, then the scotoma is probably only partly explained by the constriction. Constrictions in small branches might produce more extensive changes if produced on the background of general narrowing than if produced alone. Involvement of any one of several arterioles may cause enlargement of the blindspots. A constriction may permit the passage of

enough blood, and fast enough, so that there are no changes in the visual field. A scotoma may have resulted from a fixed lesion and be permanent in the absence of constrictions at the time of examination. The condition of the arterioles may change between the time of examination of the fundus and that of completion of the field tests (in case B they changed kaleidoscopically during the ophthalmoscopic examination). Some constrictions may have been overlooked. Some of the scotomas may have been caused by occlusion of a branch arising from the constricted wall of a larger vessel, instead of directly by partial occlusion of the vessel actually showing the constriction (see section entitled "Hypothesis That the Spasms Cause the Scotomas").

In actually making the evaluations, some of these factors presented themselves more frequently and conspicuously than others. A scotoma in an incompatible position was not considered necessarily inconsistent because, as previously stated, it might have been a fixed lesion, the result of previous constrictions. This was shown to be the fact several

TABLE 2.—*Consistency of Observations on Visual Fields with Fundi*

	Before Drugs		After Drugs	
	Number of Observations	Percentage	Number of Observations	Percentage
Consistent	70	57	21	50
Partly consistent	30	24	6	14
Inconsistent	20	16	15	35
Questionably consistent	3	2.4	0	0

times in cases observed repeatedly (page 129 and table 3). However, the absence of a scotoma where there should have been one was considered an inconsistency, despite the possible explanations described in the preceding paragraph. Large scotomas, probably too large to be completely explained by the constriction which was observed, but nonetheless partly explained by it, were considered partly consistent; it should be noted that this does not imply any inconsistency. Enlarged blindspots were considered consistent with constrictions in several different vessels. Central scotomas were deemed consistent with constrictions of the macular vessels; constrictions of those vessels without a central scotoma were called inconsistent.

The consistencies and inconsistencies are listed in table 2.

The general course of the scotomas and the constrictions was consistent over a period in the 4 cases in which four or more serial observations were made (cases 9, 10, 11 and 12). In general, scotomas and constrictions became more pronounced or less pronounced concomitantly (table 3).

TABLE 3.—*Observations in Twenty-One Cases of Multiple Sclerosis* *

Case	Age	Sex	Eye	Date	Scotomas: Normal Field	Central	Paracentral	Peripheral	Enlarged Blindspot	Contracted Field	Effect of Drug: Amyl Nitrite	Papaverine	Fundi: N	Gen	SN	IN	ST	IT	Mac	Pul	Effect of Drug: Pul	Cons	TP	Consistency: Before Drug	After Drug	Visual Acuity: Before Drug	After Drug	Shifting Scotoma	Shifting Constriction
			Group A																										
1	47	M	OD	9/29/44	..	..	..	..	+	..	..	..	..	..	..	..	..	..	+/P	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	..	+	..	..	..	..	..	..	..	..	..	+/P	..	..	..	+	+	..	20/40	.....	..	..
2	30	F	OD	3/16/44	..	..	..	..	..	+	..	..	+	..	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	..	..	+	..	..	+	..	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
3	38	F	OD	3/8/44	..	..	..	..	..	+	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	..	..	+	..	..	+	..	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
4	44	M	OD	11/24/44	..	..	..	..	..	+	—	..	..	..	..	..	..	..	P++P	..	..	—	—	+	+	20/25	20/25	..	..
			OS		..	..	..	..	+	+	—	..	..	..	..	..	..	..	P++P	..	..	—	—	+	+	20/25	20/25	..	..
5	23	M	OD	6/23/44	..	..	..	+	..	..	P	..	..	+;	P/+	..	..	..	P/+	—	+	P	—	—	P	20/20	20/20	..	..
			OS		..	+	..	+	+	..	P1,2,—3	..	..	..	P/S	..	..	..	P/S	—	+	P	—	P	P	20/100	20/50	..	..
			OD	6/30/44	+	..	..	..	..	..	..	..	..	..	..	..	..	..	P/S	..	..	..	—	—	..	20/20	.....	..	+
			OS		..	SM	..	..	..	..	..	..	..	..	..	..	..	..	P/++	..	..	..	—	+	..	20/50	.....	..	++
6	30	F	OD	9/19/44	..	..	..	..	+	..	—	..	..	..	†	..	..	..	P+P	—	+	C	+	P	+	20/20	20/20	..	..
			OS		..	..	..	+	+	..	Cl	..	..	..	..	..	..	..	P+P†	—	+	C	+	P	+	20/40	20/40	..	+
			OD	9/22/44	..	..	..	..	SM	..	..	..	..	..	†	..	..	P/H	PSP	..	..	..	+	P	..	20/30	.....	..	+
			OS		..	..	..	..	SM	..	..	..	+	..	..	..	..	..	..	..	..	..	+	+	..	20/40	.....	..	+
			OD	9/28/44	+	..	..	..	..	..	..	..	..	..	..	..	..	..	PSP L	..	..	..	+	—	..	20/30	.....	..	++
			OS		+	..	..	..	..	..	..	..	..	..	..	..	..	..	+/P +/P	..	..	..	+	—	..	20/30	.....	..	++
7	23	F	OD	11/2/44	..	..	+	..	+	..	..	..	..	..	P/H	..	..	..	..	+	..	..	+	P	..	20/20	.....	..	..
			OS		..	..	..	..	+	..	..	..	..	..	P/+	P/+	..	..	..	+	..	..	—	P	..	20/20	.....	..	..
			OD	11/21/44	..	..	SM	..	+	..	P1,—2	..	..	..	..	..	..	..	..	+	++	‡	+	+	..	20/20	20/20	..	+
			OS		..	..	..	..	+	..	—	..	..	..	..	..	..	..	..	+	++	..	—	+	+	20/20	20/20	..	++
			OD	11/24/44	..	..	R	..	..	..	..	P	..	..	..	..	..	P/+	..	..	..	—	+	—	—	20/20	20/20	..	+
			OS		+	..	..	..	..	..	..	—	..	..	P/+	..	..	..	..	..	..	—	—	—	—	20/20	20/20	..	+
8	39	M	OD	8/24/44	..	..	..	+	..	..	C	..	..	..	P/H	P/+	..	P/+	..	..	..	P	—	P	+	20/30	NR	..	..
			OS					++			C				P/+	P	P	P/+				P	—	P	+	20/20	NR	..	..

			OS		+	..	..	..	..	..	..	—	..	..	P / +	..	..	..	..	..	..	—	—	—	—	20/20	20/20	..	+
	8	39	M	OD	8/24/44	..	..	..	+	..	..	C	..	..	..	P / H	P / +	..	P / +	..	..	..	P	—	P	+	20/30	NR	..	..
				OS		..	..	..	++	..	..	C	..	..	..	P / +	P / +	P / +	P / +	..	..	..	P	—	P	+	20/30	NR	..	..
	9	36	..	OD	7/6/40	..	..	+	++	+	..	..	..	..	+	..	..	..	..	+ + / P P	..	..	..	+	P	..	20/20	.....	..	..
				OS		..	..	..	+	+	..	..	..	..	+	..	..	..	..	PSSP	..	..	..	+	P	..	20/20	.....	..	..
				OD	7/7/44	..	..	+	++	..	..	C1,—2	..	..	+	..	..	..	..	+ + / P P	—	+	C	+	P	P	20/20	20/20	..	..
				OS		..	..	..	+	..	..	—	..	..	+	..	..	..	..	PSSP	—	+	C	+	—	+	20/20	20/20	..	..
				OD	7/8/44	..	..	+	++	..	..	..	C1,P2	..	+	..	..	..	..	+ + / P P	..	..	P	+	P	P	20/20	20/20	..	..
				OS		..	..	..	+	..	..	..	—	..	+	..	..	..	..	PSSP	..	..	P	+	—	—	20/20	20/20	..	..
				OD	5/24/45	..	..	..	SM	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
				OS		..	..	..	SM	+	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	+	++
	10	31	F	OD	6/21/44	..	R	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	.....	.....	..	..
				OS		..	R	..	..	..	..	..	..	..	..	..	..	..	..	P++P	..	..	..	—	+	..	.....	.....	..	..
				OD	6/27/44	..	R	..	..	..	..	—	..	..	+	..	..	..	..	..	..	..	P	+	+	+	20/100	20/100	..	..
				OS		..	LGR	..	..	..	..	P	..	..	..	..	..	..	..	P++P	..	..	P	—	+	+	20/100	20/100	..	..
				OD	6/29/44	..	LGR	..	..	..	..	..	..	..	L	..	..	..	..	..	..	..	..	+	+	..	20/50	.....	..	..
				OS		..	SM	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	—	+	..	20/50	.....	..	++
				OD	7/7/44	..	SM	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	+	+	..	20/50	.....	..	..
				OS		..	LGR	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	—	+	..	20/50	.....	..	..
				OD	7/13/44	..	LGR	..	..	..	..	..	P	..	+	..	..	..	..	PSP	—	+	C	+	+	+	20/50	20/50	..	+
				OS		..	R	..	..	..	..	..	?	..	..	..	..	..	..	P+++P	—	+	C	—	+	+	20/50	20/50	..	+++
	11	28	..	OD	5/8/44	..	..	..	+	+	..	P1,C2	..	( )	..	..	..	..	..	..	..	..	..	..	..	..	20/40	20/40	..	..
				OS		..	..	..	++	+	..	C1,P2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	20/20	20/20	..	..
				OD	6/2/44	..	..	++	+++	SM	..	‖	..	..	‖	..	..	P / H	..	..	+	+	—1,¶	+	P	—	20/40	20/30	++	..
				OS		..	..	..	LGR	+	..	In—1,P2×	..	..	+#	..	..	..	..	**	+	+	—1	+	P	—	20/20	20/20	..	..
				OD	6/15/44	..	..	..	+++	LGR	..	††	..	..	‖	..	..	P / H	..	..	+	+	—1,¶	+	P	—	20/40	20/30	..	..
				OS		..	..	..	..	+	..	—	..	..	+#	..	..	..	..	..	+	+	—	+	P	+	20/20	20/20	..	..
				OD	6/17/44	⊃	..	..	..	..	..	None	..	..	‖	..	..	P / H	..	..	+	—	—	+	..	..	20/30	.....	..	..
				OS		..	..	..	..	..	..	None	..	..	+#	‡‡	..	..	..	..	+	—	..	+	..	..	20/20	.....	..	..
				OD	6/20/44	..	..	+	+,LGR	+	..	..	P	..	‖	..	..	P / H	..	..	+	In	P	+	P	+	20/30	20/30	+	..
				OS		..	..	+	+	+	..	..	C1,2,—3	..	+#	..	..	..	..	..	+	In	P	+	P	+	20/20	20/20	+	..
				OD	9/26/44	..	..	..	+	..	..	..	..	..	‖L	..	..	P / H L	..	..	+	..	..	+	?	..	20/30	.....	..	..
				OS		+	..	..	..	..	..	..	..	..	L	..	..	..	..	..	+	..	..	+	?	..	20/20	.....	..	+
				OD	9/29/44	..	..	+	++	LGR	..	..	..	..	§§	..	..	P / — H LGR	..	..	+	..	..	+	P	..	20/30	.....	+++	+
				OS		..	..	+	..	+	..	..	..	..	+	..	..	⊙	..	P / + P / +	+	..	..	+	P	..	20/20	.....	++	++++

TABLE 3.—*Observations in Twenty-One Cases of Multiple Sclerosis*—Continued*

Case	Age	Sex	Eye	Date	Scotomas: Normal Field	Central	Paracentral	Peripheral	Enlarged Blindspot	Contracted Blindspot	Effect of Drug: Amyl Nitrite	Effect of Drug: Papaverine	Fundi: N	Gen	SN	IN	ST	IT	Mac	Pul	Effect of Drug: Pul	Effect of Drug: Cons	TP	Consistency: Before Drug	Consistency: After Drug	Visual Acuity: Before Drug	Visual Acuity: After Drug	Shifting Scotoma	Shifting Constriction
12	30	F	z																										
			OD	4/24/44	..	..	+++	..	+	+	..	..	..	+	..	..	..	+	..	+	..	..	+	P	..	20/40	z	..	..
			OS		..	..	++	+++	+	+	..	..	..	+	..	..	..	..	..	..	..	..	+	—	..	20/40	.....	..	..
			o																										
			OD	4/24/44	..	..	SM SM	+	SM	+	..	..	..	(×)	..	..	..	..	..	..	..	..	..	..	..	..	20/40	.....	++	..
			OS		..	..	..	+	SM	+	..	..	..	(×)	..	..	..	..	..	..	..	..	..	..	..	..	20/20	.....	++++	..
			OD	5/26/44	..	..	..	+	..	..	..	LGR	..	+	..	..	..	..	..	..	..	c	+	+	+	20/30	20/20	..	+
			OS		..	△	..	..	+	..	..	P¶¶	..	+	..	..	..	..	++	..	..	−1,C2	+	P	+	15/200	20/100	+	++
			OD	6/5/44	..	..	..	+	..	..	..	C	..	+	..	..	+	+	..	?	..	—	+	P	—	20/30	20/30	..	++
			OS		..	Huge	..	..	..	..	..	P	..	+	..	..	..	..	++	?	..	−1,C2	+	+	+	2/200	4/200	+⊕	..
			OD	6/16/44	..	..	..	++	..	..	..	—	..	□□	..	..	..	..	..	..	..	—	+	—	—	20/30	20/30	+	++++
			OS		..	△	..	..	+	..	..	P¶¶—2	..	□□	..	..	..	..	..	..	..	—	+	+	—	5/200	15/200	+⊕	+
			OD	6/24/44	..	..	..	+	+	..	..	..	..	(×)	..	..	..	..	..	..	..	..	..	..	..	20/30	.....	+	..
			OS		..	△	..	..	+	..	..	..	..	(×)	..	..	..	..	..	..	..	..	..	..	..	6/200	.....	+⊕	..
			OD	6/29/44	..	..	..	..	+	..	..	..	..	+	P/+	..	..	..	..	..	..	..	+	—	..	20/30	.....	..	+++
			OS		..	+	..	..	+	..	..	..	..	L	..	..	..	..	P++	PL	..	..	..	+	P	..	20/200	.....	..	+
			OD	7/6/44	..	..	..	+	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	+	P	..	20/20	.....	+	+
			OS		..	△	..	..	..	..	..	..	..	+	..	..	..	..	S/P	S/P L	..	..	..	+	P	..	15/200	.....	+⊕	..
			OD	7/11/44	..	..	..	+	..	..	..	..	..	+	P/+	..	..	..	..	..	..	..	..	+	—	..	20/20	.....	..	+
			OS		..	⟷	..	..	..	..	..	..	..	+	P/+	..	..	..	..	..	..	..	..	+	P	..	12/200	.....	+⊕	+++
			OD	8/1/44	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	+
			OS		..	..	+	..	..	..	..	..	..	>RT	..	..	..	..	..	..	..	..	+	—	..	20/30	.....	+	+
			OD	10/3/44	+	..	..	..	..	..	..	..	..	+	..	..	..	?	..	..	..	..	+	?	..	20/20	.....	..	..
			OS		..	..	R	..	..	..	..	..	..	+	..	..	..	?	..	..	..	..	+	—	..	20/30	.....	..	..
			OD	2/19/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	+	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	+	..	..	..	..	..	+	..	..	..	P/+	..	+	..	..	+	+	..	20/20	.....	+	..
			OD	2/26/45	+	..	..	..	..	..	..	..	..	+	..	..	..	P/+	P/+ P/+	+	..	..	+	—	..	20/20	.....	..	++
			OS		..	..	R	++	..	..	..	..	..	+	..	..	..	P/+	P/+ P/+	..	..	..	+	P	..	20/30	.....	++	++
			OD	3/3/45	..	..	..	+	..	..	..	..	..	+	..	..	..	..	P/+ P/+	+	..	..	+	—	..	20/20	.....	..	..
			OS		..	..	R	++	..	..	..	..	..	+	..	..	..	P/H	..	+	..	..	+	P	..	20/30	.....	..	..
			OD	3/19/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/30	.....	..	++
			OS		..	..	..	++	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/30	.....	..	+
			OD	3/29/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	SM SM	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..

			OD	3/19/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/30	.....	..	++
			OS		..	..	..	++	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/30	.....	..	+
			OD	3/29/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	SM SM	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OD	4/14/45	..	..	..	++	..	..	..	..	..	+	..	..	..	..	..	+	..	..	+	+	..	20/20	.....	++	..
			OS		..	..	..	++	+	..	..	..	..	+	..	..	..	..	..	+	..	..	+	+	..	20/30	.....	+	..
			OD	4/20/45	..	..	..	++	..	..	..	..	..	+	..	..	..	..	..	?	..	..	+	+	..	20/30	.....	..	..
			OS		..	..	..	++	SM	..	..	..	..	+	..	..	..	..	..	?	..	..	+	+	..	20/30	.....	..	..
			OD	4/27/45	..	..	..	+	+	..	..	..	..	+	..	..	..	..	..	+	..	..	+	+	..	20/30	.....	..	..
			OS		..	..	..	SM	..	..	..	..	..	+	..	..	..	..	..	+	..	..	+	+	..	20/30	.....	..	..
			OD	5/4/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	+LGR	LGR	..	..	..	..	+	..	..	..	..	+ / P + / P	..	..	..	+	P	..	20/20	.....	++	++
			OD	5/8/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	++	..	..	..	..	..	+	..	..	..	..	H / P	..	..	..	+	—	..	20/20	.....	..	+
			OD	5/15/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	++	+	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/30	.....	+	..
			OD	5/22/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	+++	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/30	.....	+	..
			OD	5/29/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		..	..	..	++	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OD	6/5/45	+	..	..	..	..	..	..	..	..	+	..	..	..	..	++	+	..	..	+	—	..	20/20	.....	..	++
			OS		..	..	..	+LGR	..	..	..	..	..	+	..	..	..	..	++	+	..	..	+	—	..	20/20	.....	..	++
	13	42	M	OD	3/2/44	+	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
				OS		..	..	..	+	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/20	.....	..	..
				OD	3/3/44	..	..	..	+	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	+	..
				OS		..	..	..	+	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/20	.....	..	..
				OD	3/7/44	..	..	..	+	..	..	>—	..	+	..	..	..	..	..	..	..	—	+	+	+	20/20	20/20	..	..
				OS		..	..	..	+	..	..	LGR	..	+	..	..	..	..	..	..	..	—	—	+	—	20/20	20/20	..	..
				OD	3/14/44	..	..	..	+	..	..	..	..	NR	..	..	..	..	..	..	..	..	+	..	..	20/20	.....	..	..
				OS		..	..	..	+	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/20	.....	..	..
				OD	3/16/44	..	..	..	..	..	..	> LGR	..	+	..	..	..	..	..	..	..	<	+	+	—	20/20	20/20	..	..
				OS		..	..	..	..	..	..	LGR	..	+	..	..	..	..	..	..	..	—	—	+	—	20/20	20/20	..	..
				OD	3/21/44	+	..	..	..	..	..	> ▲	..	+	..	..	..	..	..	..	..	←	+	+	P	20/20	20/20	..	..
				OS		..	..	..	+	..	..	LGR	..	+	..	..	..	..	..	..	..	←	—	+	P	20/20	20/20	..	..
				OD	5/4/44	..	..	..	+	..	..	>LGR	..	+	..	..	..	..	..	..	..	<	+	+	—	20/20	20/20	+	..
				OS		..	..	..	+	..	..	LGR	..	+	..	..	..	..	..	..	..	<	—	+	—	20/20	20/20	..	..
				OD	6/13/46	+	..	..	..	..	..	>—	..	+	..	..	..	..	..	..	..	↓	+	+	—	20/20	.....	..	..
				OS		+	..	..	..	..	..	—	..	+	..	..	..	..	..	..	..	—	—	+	+	.....	.....	..	..
			Group B																													
	14	20	F	OD	4/27/45	..	..	..	..	..	..	..	..	..	+	#	..	..	..	+ / P	..	..	..	+	..	..	.....	.....	..	..
				OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	..	..	.....	.....	..	..
				OD	5/11/45	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	..	..	.....	.....	..	++
				OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	..	..	.....	.....	..	..
				OD	5/28/45	..	..	..	..	..	..	..	..	..	+	..	..	..	P+++P	..	..	..	..	+	..	..	.....	.....	..	+++
				OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	..	..	.....	.....	..	..
				OD	6/11/45	..	..	..	..	..	..	..	..	..	+	..	..	..	..	+	..	..	..	+	..	..	.....	.....	..	+++
				OS		..	..	..	..	..	..	..	..	..	+	..	..	..	#	+	..	..	..	—	..	..	.....	.....	..	++
				OD	6/19/45	..	..	..	..	..	..	..	..	..	+	..	..	..	..	+	..	..	..	+	..	..	.....	.....	..	..
				OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	+	..	..	..	—	..	..	.....	.....	.	..
				OD	3/11/46	..	..	..	..	..	..	>	..	..	+	..	..	..	..	—	+★	..	..	+	..	..	.....	.....	..	..
				OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	—	+★	..	..	—	..	..	.....	.....	..	..

TABLE 3.—*Observations in Twenty-One Cases of Multiple Sclerosis*—Continued*

Case	Age	Sex	Eye	Date	Scotomas: Normal Field	Central	Paracentral	Peripheral	Enlarged Blindspot	Contracted Blindspot	Effect of Drug: Amyl Nitrite	Effect of Drug: Papaverine	Fundi: N	Gen	SN	IN	ST	IT	Mac	Pul	Effect of Drug: Pul	Effect of Drug: Cons	TP	Consistency: Before Drug	Consistency: After Drug	Visual Acuity: Before Drug	Visual Acuity: After Drug	Shifting Scotoma	Shifting Constriction
			OD	3/12/46	..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	+	++	●	+	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	+	++	●	—	..	..	.....	.....	..	..
			OD	3/15/46	..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	..	+	—	..	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	..	+	■	..	..	..	.....	.....	..	..
			OD	3/21/46	..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	..	+	—	..	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	..	+	◦	..	..	..	.....	.....	..	..
			OD	3/25/46	..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	—	+	—	+	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	—	+	◊	—	..	..	.....	.....	..	..
			OD	4/9/46	..	..	..	..	..	..	>	..	..	+	..	..	..	..	..	..	+	..	..	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	+	..	..	..	..	.....	.....	..	..
			OD	4/12/46	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	—	+	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	—	—	..	..	.....	.....	..	..
15	29	F	OD	11/4/44	..	..	..	..	..	..	..	..	..	..	H/P	H/P	..	..	+/P	..	..	..	..	—	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	..	H/P	..	..	..	..	—	..	..	.....	.....	..	..
			OD	11/10/44	..	..	..	..	..	..	..	..	..	..	H/P	H/P	..	..	+/P	..	..	..	..	—	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	..	H/P	..	..	..	..	—	..	..	.....	.....	..	..
			OD	5/25/45	..	..	..	..	..	..	..	..	..	..	H/P	H/P	..	..	+/P	..	..	..	..	—	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	..	H/P	..	..	..	..	—	..	..	.....	.....	..	..
16	37	F	OD	1/8/46	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	S/P	S/P	..	+	..	?	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	S/P	S/P	..	+	..	—	..	..	.....	.....	..	..
			OD	1/22/46	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	S/P	S/P	..	+	..	?	..	..	.....	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	S/P	S/P	..	+	..	—	..	..	.....	.....	..	..
17	33	F	OD	11/21/44	..	..	..	..	..	..	..	..	..	..	..	..	..	..	H/P	..	..	..	..	..	+	..	..	20/100	.....	..	..
			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	..	H/P	..	..	..	..	..	+	..	..	20/200	.....	..	..
			OD	11/24/44	..	..	..	..	..	..	..	..	..	..	..	..	..	H/P	H/P	H/P	++	..	..	P	+	..	..	20/200	20/200	..	+++

			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	$\frac{H}{P}$	..	..	..	..	+	..	..	20/200	.....	..	..
			OD	11/24/44	..	..	..	..	..	..	..	..	..	..	..	..	..	$\frac{H}{P}$ $\frac{H}{P}$ $\frac{H}{P}$	++	..	..	P	+	..	..	20/200	20/200	..	+++
			OS		..	..	..	..	..	..	..	..	..	..	..	..	..	$\frac{H}{P}$	..	..	..	P	+	..	..	20/200	20/200	..	..
			Group C																										
18	25	F	OD	4/24/44	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/20	.....	..	..
			OS		+	..	..	..	..	..	..	..	..	..	..	..	..	..	$\frac{+}{P}$ $\frac{+}{P}$	..	..	..	—	—	..	20/20	.....	..	..
19	54	M	OD	3/7/44	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/15	.....	..	..
			OS		+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/20	.....	..	..
20	37	M	OD	3/25/44	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
			OS		+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	+	+	..	20/20	.....	..	..
21	21	F	OD	8/17/44	+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/20	.....	..	..
			OS		+	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	—	+	..	20/20	.....	..	..

A plus sign in any of the columns under "Scotoma" means that the indicated scotoma existed. The number of plus signs denotes the number of scotomas of that particular kind found in a given observation. R indicates relative scotoma; SM, a smaller scotoma; LGR, a larger scotoma.

* Under "Fundi," N means normal blood vessels; Gen, generalized narrowing; SN superior nasal arteriole; IN, inferior nasal arteriole; ST, superior temporal arteriole; IT, inferior temporal arteriole; Mac, macular arterioles; Pul, pulsation; Cons, constrictions; TP, temporal pallor. Plus signs in the blood vessel columns under "Fundi" indicate presence of constrictions; S means segmented constriction; H, hourglass constriction; +, a constriction which was neither S nor H. P refers to the papilla; when symbols appear over the P, the constriction was on the papilla; when they appear under the P, the constriction was off the papilla; when they appear between two P's, the constriction was both on and off the papilla. L means a less pronounced constriction. The number of plus signs in the Mac column denotes how many macular arterioles were involved.

Each symbol stands for something separate; i. e., for case 12, 5/4/45, OS, "Peripheral" column, the + sign means a new peripheral scotoma, and LGR, enlargement of the old one, marked as smaller (SM) in previous observation (4/27/45).

In columns denoting the effects of drugs, — means no effect; P, partial relief; C, complete relief, and In, increase in size. Numbers in these columns refer to the box (box 1, 2, etc.) in which a positive effect was noted; the effect of the drug is denoted first, and then the box number.

In the columns "Shifting Scotoma" and "Shifting Constriction," the number of plus signs denotes the number of shifting scotomas or shifting constrictions.

† The superior nasal venule showed constriction (off papilla).

† One arteriole opened and closed, becoming alternating white and pink synchronously with the pulse. This vanished after administration of amyl nitrite. The vessel then merely pulsated.

‡ General retinal vasodilatation occurred, but was least at the arteriolar bifurcation at the lower pole of disk; a constriction was observed in this position (inferior temporal arteriole) three days later (11/24 in table).

NR means not recorded.

§ Complete relief of the two paracentral scotomas; partial reduction of the two peripheral scotomas, one just above, and one just lateral to the blindspot; the other peripheral scotoma (top of field) and the enlarged blindspot were unchanged.

‖ Generalized constriction, especially of the smaller arterioles.

¶ Extension of the hourglass constriction.

× The peripheral scotoma which increased in size was at the top of the field.

A cilioretinal arteriole was present, contained a constriction and was pulsating.

** The macular arterioles showed segmented constrictions after, but not before, medication.

†† A new peripheral scotoma, near the top of the field, was completely relieved; other (old) peripheral scotomas, one at the top of the field and one lateral to the blindspot, were unchanged; the blindspot was unchanged.

⊃ Not examined. ‡‡ Superior nasal arterioles showed segmented constrictions after administration of amyl nitrite, but not before. §§ All arterioles adjacent to the nasal side of the disk were constricted. ⊙ The superior division of the central retinal arteriole presented an hourglass constriction.

z During spontaneous attack. ○ Attack subsiding, four hours later. △ Bizarre scotoma, including the central scotoma (fig. 3). □ Before drug administration in the right eye, the macular arterioles are greatly constricted. The nasal division of the superior nasal arteriole, by contrast with the temporal division, shows marked constriction; the nasal branch presents a whitish appearance for about 1 disk diameter. The three branches of the inferior division show moderate constriction; the most temporal is the most constricted, alternately filling and closing with the pulse. In the left eye, the macular arterioles are in a constricted state. The superior temporal venule presents a dilated bulbous appearance where it crosses the arteriole, extending distally and proximally about 1 disk diameter. The inferior temporal arteriole shows a prominent constriction on the papilla (c) as it emerges from under the corresponding venule. After the intravenous injection of papaverine hydrochloride, the venules become so large and distended as to suggest varices. All the retinal arterioles dilate, but the areas of previously described constriction are still much in evidence. ¶¶ The part which remained was a small central scotoma (fig. 3). ⊕ Striking change in size and shape. ←→ Two bizarre scotomas starting at the periphery and crossing the point of fixation.

> A hot drink was taken (usually tomato soup). < Segmented constrictions of the macular arterioles appeared, and the whole arteriolar tree became narrowed. ▲ A small peripheral scotoma, seen at other examinations but not on March 21 prior to the drink, appeared after the drink. ← General constriction of all the arterioles, most prominent in the left macular arterioles. ↓ Constriction in the medial division of the inferior temporal arteriole. ϕ During the examination, two divisions of the inferior temporal arteriole became greatly constricted, becoming practically colorless. ★ After the hot drink, pulsations included venules as well as arterioles. ● After the hot drink, the inferior temporal arterioles of the right eye each contained an area of constriction both on and off the papilla; the inferior temporal arteriole of the left eye contained an area of marked constriction about 2 disk diameters away from the papilla. ■ After the hot drink, the inferior temporal arteriole in the left eye contained a constricted area. ◇ After the hot drink, the inferior temporal arteriole in the left eye was constricted in an area about 2 disk diameters away from the papilla. ◊ After the hot drink, two constricted areas were seen in the superior temporal arteriole of the left eye (one on and the other just off the papilla), and two branches of the inferior temporal arteriole showed segmented constrictions on and off the papilla.

Greatly decreased visual acuity was always associated with a central scotoma.

The consistencies and inconsistencies of changes in visual acuity with changes in scotomas are to be found in the data in table 1. Observations 1, 4, 6, 7 and 8 showed consistency, and observation 2 perhaps did. Observations 3 and 5 did not.

CONTROL OBSERVATIONS

There appeared to be no way in which to control the essential feature of these observations. Studies of patients with other diseases, whatever they showed, would not alter the basic hypothesis concerning multiple sclerosis which may be derived from these investigations. Hence, our full attention was devoted to cases of multiple sclerosis.

TABLE 4.—*Summary of Observations on Vasospasm and Scotoma in Twenty-One Cases of Multiple Sclerosis*

Observation	Number of Observations		
Hourglass constrictions	12		
Segmented constrictions			
Before drugs	10		
After drugs only	6		
Shifting scotomas	38		
Shifts in constrictions	77		
Constrictions affected by	—	P	C
Amyl nitrite	9 (26%)	19 (54%)	7 (20%)
Papaverine hydrochloride	6 (33.3%)	6 (33.3%)	6 (33.3%)
Scotomas affected by			
Amyl nitrite	18 (46%)	10 (25%)	11 (28%)
Papaverine hydrochloride	5 (24%)	12 (57%)	4 (17%)

One feature which does require control relates to the matter of general change in blood flow. Are the shrinkages of the scotomas specifically related to the relaxations of the constrictions, or might the same result follow a mere general increase in blood flow to the impaired part? This question appears to be answered in favor of the first alternative by the fact that many scotomas did not become reduced in size after administration of a drug. The reader is referred to the previous discussion of fixed and transient scotomas in this connection.

A possible defect in this reasoning is that, while many of the scotomas appear to result from vasoconstrictive disturbances in the retina itself, some may depend on vasoconstrictive disturbances in other portions of the visual system. Supposedly, the same reasoning would apply to disturbances anywhere, but it is conceivable that it is applicable to the vasoconstriction in the retina alone and that the scotomas which did not respond to drugs may have arisen from vasoconstriction in other parts of the visual system, which might, perhaps, have some other sort of vascular arrangement.

Many other studies of many kinds obviously are indicated for the purpose of throwing more light on the effects of vasospasm in a variety of circumstances. From such sources, it may be possible to add to the understanding of the type of phenomena here described as occurring in multiple sclerosis.

The results of study for all cases described so far except those for cases A and B are recorded in table 3 and summarized in table 4.

ADDITIONAL OBSERVATIONS

THE EYES

Veins.—Attention should be called to case 6, in which the right superior nasal vein twice showed a constriction. This is in accord with the observations of Rucker.[4]

Acute Dilatation of a Vein.—An observation worthy of remark was made in case 12 on June 15, when some of the veins of the left retina became so large after an injection of papaverine hydrochloride that they gave the appearance of varicosities. These veins soon receded to their usual size, which was possibly slightly greater than normal.

Filling and Emptying.—The phenomenon of alternate filling and emptying of a single arteriole, noted in cases 6 and 12, was also seen in case 17 during a period in which the patient was at the Mount Sinai Hospital. The resident in neurology, Dr. Richard Drooz, and one of us (R. M. B.) examined her fundi, and each independently saw the left inferior nasal arteriole undergoing this process, exactly as described in cases 6 and 12 except that the rhythm was slow and irregular and not synchronous with that of the pulse.[5] In 2 other instances (cases 13 and 14, table 3; footnote for June 11, 1945) the caliber of vessels was seen to change during the ophthalmoscopic examination.

Slight Changes in Advance of Overt Constriction.—In case 7, on Nov. 21, 1944, general retinal vasodilatation followed the inhalation of amyl nitrite. The dilatation was least noticeable at a place where an actual constriction was seen three days later (on November 24), although none had been observed there prior to the administration of the drug. Possibly slight constrictive changes, not visible under ordinary conditions, had begun to occur on November 21.

Diplopia.—Four cases with early or transient diplopia were observed.

Case 2.—The patient had as one of her complaints diplopia on awakening every morning. It persisted for several hours and then disappeared. She was

4. Rucker, C. W.: Sheathing of the Retinal Veins in Multiple Sclerosis, J. A. M. A. **127**:970 (April 14) 1945.

5. Franklin, C. R., and Brickner, R. M.: Acute Alterable States in Multiple Sclerosis, Arch. Neurol. & Psychiat. **55**:418 (April) 1946.

seen on the morning of March 1, 1944, while the diplopia was present. Two whiffs of amyl nitrite were administered, and, according to the patient's subjective observation, the diplopia disappeared.

Case C.—A white man aged 29 with early multiple sclerosis had as one of his symptoms morning diplopia in the right upper quadrant of his visual field. On April 24, 1945 the images were plotted. The patient was then given two whiffs of amyl nitrite. Immediate replotting of the fields showed that the diplopia had disappeared, the images now being superimposed. By June 27 the diplopia had

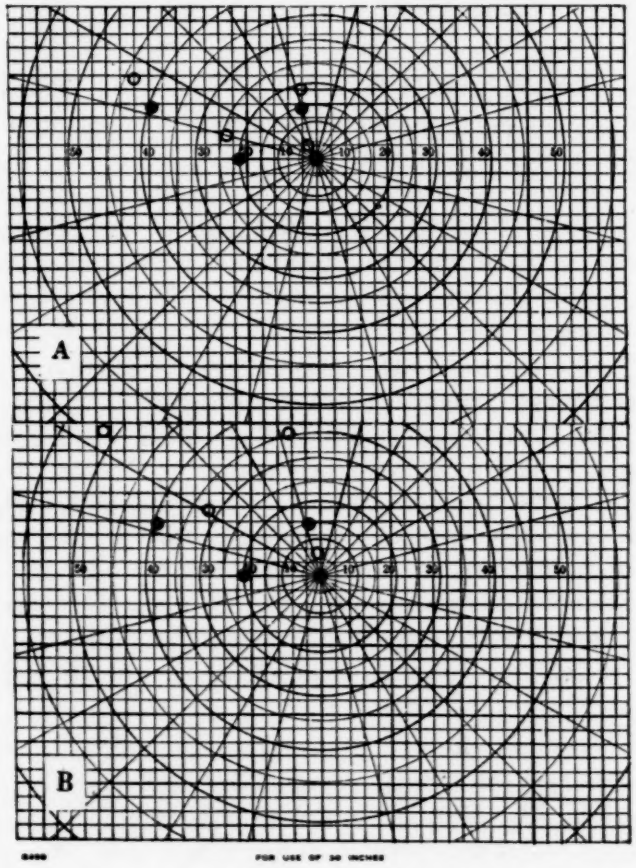


Fig. 6.—Improvement in diplopia following amyl nitrite in a patient with pronounced paresis of the left superior rectus muscle. *A*, before and *B*, after administration of amyl nitrite. Fields were taken at a distance of 30 inches (76 cm.), with red glass over the left eye. No diplopia was detected in any other part of the fields. The solid circles represent the real images; the rings, the false images.

increased in degree. Inhalation of amyl nitrite resulted in improvement, but not in disappearance, of the diplopia.

Mere decrease in the degree of diplopia, with some residual, fixed diplopia, may well be compared with the scotomas previously discussed, in which the drugs produced a reduction in size, leaving unaffected a fixed, residual scotoma. This comparison is especially pertinent in view of the earlier test in case C, in which

the diplopia was abolished completely (but transiently) with amyl nitrite. The hypothesis is suggested that the constrictions of vessels which produced the earlier diplopia finally resulted in a fixed lesion and that additional diplopia then developed as a consequence of additional vasoconstriction, which had not yet produced a fixed lesion. The fixed lesion showed itself as the residual, unaffected diplopia on June 27, and the new diplopia, not yet representing a fixed lesion, revealed itself as the component which was affected by the drug on that date.

CASE D.—A white woman aged 21, referred by Dr. Joseph Laval, was having her first attack of multiple sclerosis; the onset had occurred one week previously. She had had diplopia for three days. The patient was referred back to Dr. Laval, who plotted the diplopia before and after a subcutaneous injection of histamine diphosphate (0.001 Gm.) and found a decrease in the degree of diplopia following the administration of the drug.

CASE E.—A white girl of 18 years, referred by Dr. Ludwig Chiavacci, seen early in her second attack of multiple sclerosis, had had her first diplopia for two weeks. The symptom was due to extreme paresis of the left superior rectus muscle. Inhalation of three whiffs of amyl nitrite reduced the diplopia to about one-third its original range (fig. 6).

IMPAIRMENT OF VISION BY HEAT AND BY EATING

CASE 13.—A white man aged 42, a dentist, stated that his vision became impaired after drinking anything hot. He was examined several times immediately after drinking hot soup. Vision became impaired subjectively. On 6 of these occasions (counting each eye) constrictions were seen, although the vessels had presented a normal appearance before (table 3). No notable changes in the visual fields were detected, however; his small peripheral scotomas frequently became larger, but this was probably not sufficient to account for the subjective complaint. These slight changes in the fields were completely or partially consistent with the arteriolar changes in only 4 of 10 observations (counting each eye). No objective decrease in visual acuity occurred at all.

The patient also stated that the mere eating of food sometimes impaired his vision slightly.

CASE F.—A white woman aged 30 with multiple sclerosis informed us that she had occasionally experienced transient reduction and blurring of vision while under a hot hair dryer. This statement was not tested objectively.

CASE 14.—The history was similar to that in case 13. Hot drinks, and the eating of food to a slighter degree, frequently increased the patient's chronic impairment of vision. The visual fields could not be adequately tested in this case either before or after the taking of the hot drink because of lack of cooperation. However, the changes in the retinal arterioles were striking (table 3). Arteriolar pulsation also increased, or appeared freshly, after the drinking in this case.

INTENTION TREMOR

CASE 20.—A white man aged 35, a heavy drinker, had multiple sclerosis; included in his symptoms was a bilateral intention tremor, which had been present for an indeterminate period. He stated that the tremor usually became worse for a few minutes after smoking a cigaret, but only if he had been drinking steadily. If he had had no alcoholic liquor for two weeks, the cigaret had no effect on the tremor. On the other hand, he stated that four drinks in immediate association

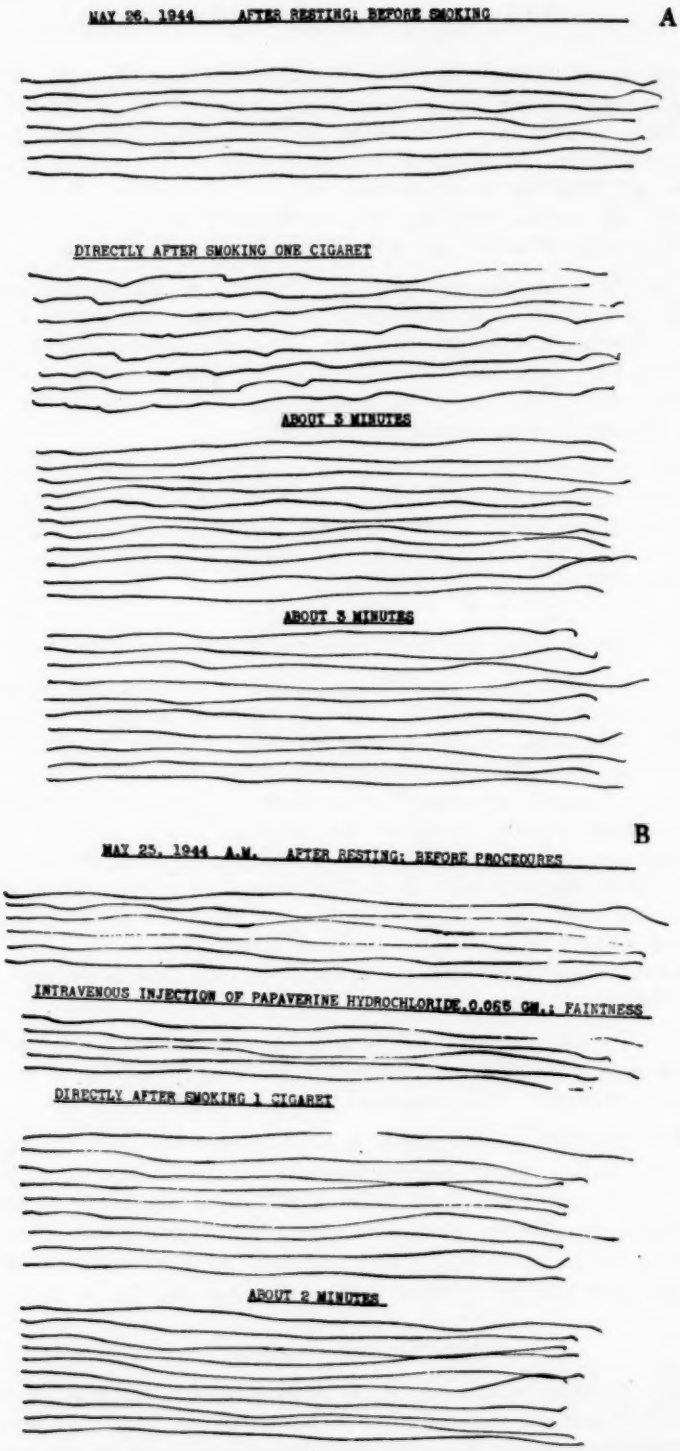
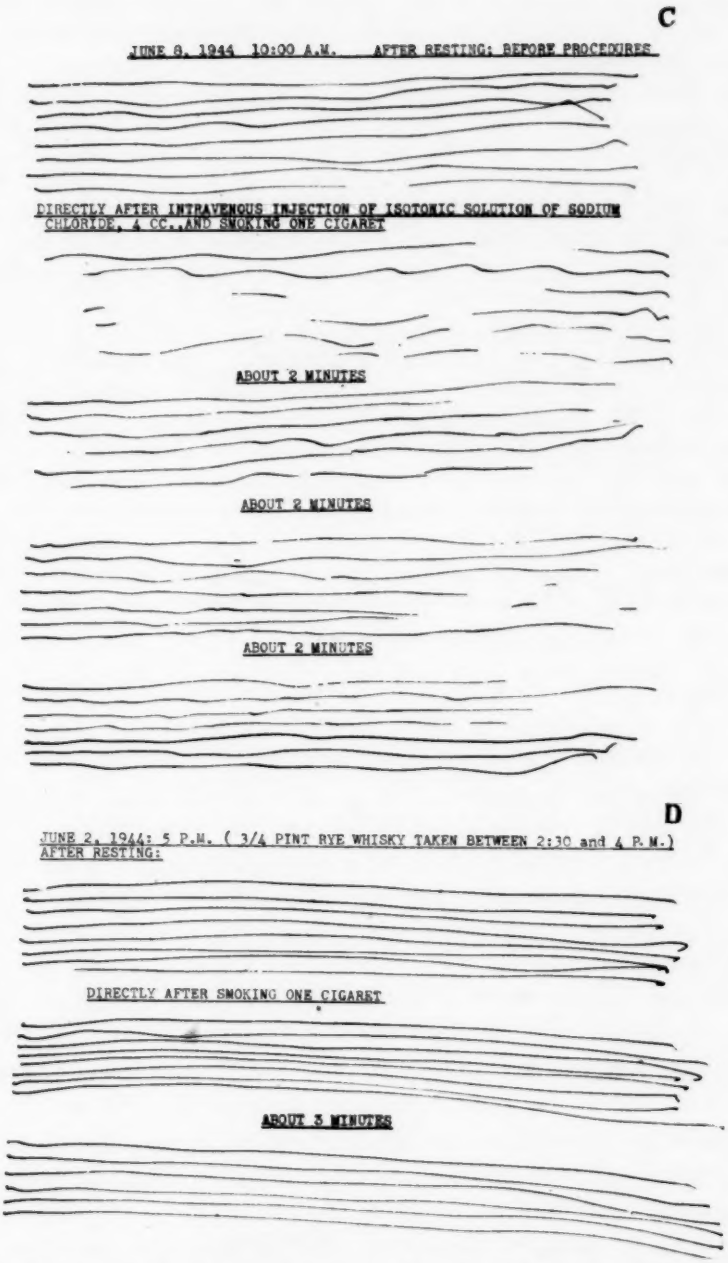


Fig. 7 (case 20).—Intention tremor involving both upper extremities, illustrated for the right upper extremity by drawing lines. *A*, increase in the tremor following the smoking of a cigaret. *B*, prevention of the effect shown in *A* by preliminary injection of 0.065 Gm. of papaverine hydrochloride; after the injection, and also after the smoking, the tremor is the same as that before either procedure.



C, control observation, with the injection of isotonic solution of sodium chloride. The increase in the tremor following the smoking of the cigaret is pronounced. *D*, effect of imbibing ¾ pint (375 cc.) of rye whisky before the test. The tremor is improved, and the smoking had no effect.

with the cigaret prevented the effect. The patient also stated that his imbalance of gait improved greatly when he was under the influence of liquor but that it was worse the day after.

Tests were conducted on the tremor and the manner in which smoking affected it. The patient, always after drinking steadily, would come to the office of one of us (R. M. B.), rest in a chair for half an hour and then demonstrate the tremor of the right upper extremity by drawing lines across a page with a fountain pen. He then smoked a cigaret, after which he resumed the drawing of lines (fig. 7 *A*). An immediate increase in tremor was apparent; subsequent series of lines drawn at one minute intervals showed a prompt waning of the effect until, in about five minutes, it was gone.

The effect was too transient to permit of attempts to relieve it with vasodilating drugs, but papaverine hydrochloride (0.0325 Gm.), introduced intravenously immediately before the smoking of the cigaret, prevented the increase in the tremor (fig. 7 *B*). There was no change in the tremor as a result of the procedure of injection. These tests were repeated many times. In a control test, in which isotonic solution of sodium chloride was administered instead of the papaverine hydrochloride which the patient thought he was receiving, the accentuation of the tremor occurred as usual after the cigaret (fig. 7 *C*).

Imbibition of 1 pint (500 cc.) of rye whisky just before the test not only prevented the effect of the cigaret but abolished the tremor altogether (fig. 7 *D*).

Case G.—A white man aged 42 with multiple sclerosis also showed an increase in intention tremor on smoking a cigaret. Circumstances prevented his being tested with drugs.

LITERATURE ON RETINAL VASOCONSTRICTION

The literature on constrictions of the retinal arterioles is fairly large. It will not be reviewed here, since its only relevance to the present investigation is to show that constrictions have been seen by other observers, associated with many diseases, chiefly hypertension, arteriosclerosis and toxemia of pregnancy. In connection with the last-mentioned condition, it is worth remembering that pregnancy (not necessarily complicated by toxemia) often brings on or accentuates attacks of multiple sclerosis. Constrictions have also been observed in cases of Raynaud's disease and of thromboangiitis obliterans (Buerger's disease).

Apparently, constrictions of retinal arterioles associated with multiple sclerosis have not been reported by other authors. Rucker [4] described and published photographs of hourglass constrictions in retinal veins in several cases of multiple sclerosis. In his cases no association with scotomas or other visual symptoms was reported and no tests with drugs were mentioned. Rucker [4] also described sheathing of the veins in 34 cases in 21 of which the presence of multiple sclerosis was established and in 7 more of which that disease was suspected. We are able to confirm this observation. Rucker's studies and ours were conducted

independently, and we were unaware of his observations until some time after his report appeared.

Recently, Zeligs [6] has stressed the importance of emotional tension in producing macular lesions in young Marines, supposedly on the basis of vasospasm. Such tension has a profound, precipitating effect in cases of multiple sclerosis, as has been pointed out by several observers (Brickner and Brill [7]). At least 1 patient in the present series (case A) described specifically his sudden attacks of unilateral blindness as sometimes resulting from sudden emotional tension.

There are a few reports of spasms with visual impairment in persons of ages ranging from 14 to 42 years without evidence of vascular disease or other known cause.[8] Possibly these are related to our own observations. Although in none of the reported cases is multiple sclerosis said to have existed, we think it is pertinent to mention the possibility of this diagnosis. In Crisp's case [8a] the attack followed a long automobile drive, something which has also been reported to occur in cases of multiple sclerosis. Pines [8f] reported retinal vasospasm in "normal" young persons, but no studies of visual function were carried out.[8]

COMMENT

The plotting of visual fields is a subjective procedure, and it is always possible for errors to occur. We believe that our results are dependable because (1) the plotting was done by highly experienced testers, (2) the results were consistent, (3) the presence or absence of scotomas coincided almost uniformly with the patients' subjective experiences, (4) scotomas were consistent with visual acuities and (5) the tests were performed on highly cooperative, intelligent patients.

NATURE OF THE CONSTRICTIONS

The transient character of many of the constrictions suggests that they are spasms. They were present at one examination and absent, or

6. Zeligs, M. A.: Central Angiospastic Retinopathy: A Psychosomatic Study of Its Occurrence in Military Personnel, Psychosom. Med. **9**:110 (March-April) 1947.

7. Brickner, R. M., and Brill, N. Q.: Dietetic and Related Studies on Multiple Sclerosis, Arch. Neurol. & Psychiat. **46**:16 (July) 1941.

8. (*a*) Crisp, W. H.: Spasm of the Retinal Arteries, Am. J. Ophth. **4**:188, 1921. (*b*) Halbertsma, K. T. A.: Un cas de spasme de l'artère centrale de la rétine, Ann. d'ocul. **163**:641, 1926. (*c*) Hairi, H.: Le spasme de l'artère centrale de rétine et l'obstruction consecutive de l'artère temporale inférieure, ibid. **163**:662, 1926. (*d*) Sédan, J., and Jayle, G.: Considèrations sur les spasmes de l'artère centrale de la rétine, Ann. d'ocul. **173**:609, 1936. (*e*) Wagener, H. P.: Significance of Spasm in Retinal Arteriolar Disease and in Retinitis, Tr. Pacific Coast Oto.-Ophth. Soc. **24**:165, 1939. (*f*) Pines, N.: The Diagnostic and Clinical Value of Some Forms of Retinal Angio-Spasm, Brit. J. Ophth. **30**:470, 1946.

present in another arteriole, at another. Sometimes they appeared suddenly, as in cases A, B and 12, and disappeared in a few minutes. Moreover, some of them had an hourglass form. In case B constrictions fluctuated kaleidoscopically while being watched. Hereafter the constrictions will be referred to as spasms.

Narrowing of arterioles is an almost universal finding in association with atrophy of the optic nerve. This, however, is a generalized narrowing, involving all the arterioles. We have observed such general narrowing in some of the cases in this series, in some, but not in all, of which there was temporal pallor. There was evidence that general narrowing may sometimes be the result of spasms; it was decided, however, not to count it among the phenomena of spasm because the evidences were sparse and incomplete. Several factors distinguish the spasms we are reporting from this type of narrowing: (1) their involvement of single arterioles; (2) their presence in some instances without any temporal pallor which can be recognized, and (3) the factors mentioned in the preceding paragraphs—the transient character and the occasional hourglass form of the spasms and the continuous observed fluctuations in some cases.

There is some evidence in case 11 that fixed changes can occur in the walls of vessels as a result of spasm. The same constrictions were seen in the same positions for many months. The paradoxic reaction to vasodilating drugs also suggests a change of some kind in the structure of the vessel.

HYPOTHESIS THAT THE SPASMS CAUSE THE SCOTOMAS

The hypothesis that the reducible scotomas result from a reduction in blood supply caused by the spasms arises from the data, in view of (*a*) the coexistence of spasms and scotomas and the high level of consistency between them (table 2), and (*b*) the usually simultaneous effect on spasm and scotoma of vasodilating drugs.

Also supporting the hypothesis that the spasms may cause a sufficient reduction in blood flow to affect function are the 3 cases in which alternating emptying and filling of an arteriole were observed. No blood could be seen in the vessel during the empty phases, and the vessel could be identified at such times only by its blood-filled proximal portion. If such a condition were prolonged, function, as well as the metabolism of tissue, would by necessity be impaired.

Still further evidence that the spasms have an effect on visual function is found in the effect of the drugs on visual acuity in some cases.

It has already been mentioned that few spasms occlude the vessel completely. Almost always blood was visible in the vessel distal to the spasm, indicating that the scotoma cannot be the consequence of com-

plete deprivation of blood in that portion of the retina supplied directly by the vessel showing the spasm. It could mean (*a*) that localized portions of the retina are completely deprived of the blood coming from a branch of the arteriole showing the spasm, that branch arising from the spastic area and having its mouth occluded by the spasm in the wall of the parent vessel (fig. 8). This branch, being small and empty of blood, might not be visible on ophthalmoscopic examination. It could also mean (*b*) that the mere reduction of blood flow in the spastic vessel itself was sufficient to impair the function of that portion of the retina supplied directly by that vessel; (*c*) that the spasm disturbed the normal pulse of the blood in the distal part of the vessel, thus impairing the normal time relationships in the distribution of blood to tissue, and (*d*) that there was capillary collapse, due to locally reduced blood pressure.

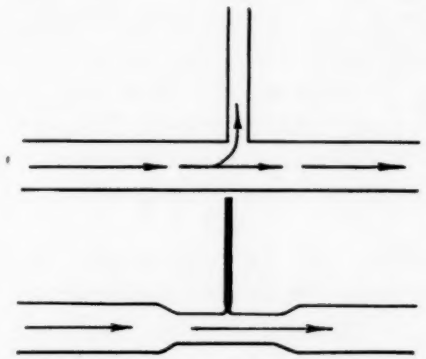


Fig. 8.—Diagram illustrating the hypothesis that small arterioles arising from a spastic, but not completely occluded, parent vessel may be completely occluded. The arrows indicate the direction of blood flow.

There are two weak links in the chain of evidence in support of this hypothesis. Although an explanation can be evoked for each of these objections they should be recognized as weaknesses at this point and be subjected to further observation. The first objection is that in some cases a reducible scotoma was in the wrong position to be explained by a given spasm. The other is that in these same instances there was, of course, no scotoma in the area indicated by the recognized spasm. The seemingly most reasonable explanations are given in the discussion on consistencies.

The rest of the accumulated evidence is sufficiently strong and consistent to warrant consideration of the hypothesis stated.

PULSATIONS

Pulsations of the entire arterial tree, synchronous with the rhythm of the cardiac pulse, were seen frequently, sometimes prior to and

sometimes after administration of the drug. No relation between pulsations and visual disturbances was found. None of the patients had glaucoma or cardiovascular disease. The pulsations are thought to reflect a change in vasomotor function which is not understood.

REVERSIBLE DISTURBANCE OF FUNCTION AND FIXED LESIONS

The rest of the discussion will be based on the hypothesis stated in the previous section.

The evidence suggests that two types of disturbances may, presumably, result from the spasms—one that is immediately reversible, in that it may be relieved by reduction of the spasm, and one not immediately reversible (fixed lesion). According to the hypothesis, if the spasm shuts off enough blood for a sufficiently long time, an actual lesion in the retina may result; this lesion is not reversible by reduction of the spasm, although it may ultimately heal by other processes.

This is illustrated by case 12 (and others). In case 12, the patient's central scotoma lasted about six weeks, when it disappeared. It was never affected by use of papaverine hydrochloride, although the shifting scotoma around and often coalescent with it was affected. The larger scotoma was always abolished, whereas the fixed, central scotoma was not, and the latter stood out alone in fields plotted after administration of the drug.

The hypothesis is that the fixed, central scotoma represented a fixed lesion in the retina, which presumably had resulted from a vasospasm either more complete or of longer duration than the spasms responsible for the reducible scotoma. The reducible scotoma is interpreted as a consequence of transient or incomplete spasm which permitted the passage of enough blood, promptly or swiftly enough, to preserve the life of the tissue, but which, nonetheless, impaired function; the dilation of the vessel by the drug permitted the temporary reestablishment of normal nutritional conditions and the disappearance of the reducible scotoma.

RELATION TO THE PATHOGENESIS OF MULTIPLE SCLEROSIS

The hypothesis that the lesions of multiple sclerosis result from vasospasm emerges naturally from these observations. This hypothesis refers not only to disturbances affecting vision but to all the disturbances and lesions in the central nervous system, as suggested by the observations on diplopia and on intention tremor.

The observations reported here suggest that many of the scotomas associated with multiple sclerosis arise from disturbances in the retina itself. Obviously, this explanation does not preclude the possibility that some scotomas may result from disturbances in other parts of the visual system. All reasoning which we have applied to the findings is intended

to apply with equal validity to any part of the nervous system, not merely to the retina, on the assumption that the vascular conditions are the same in the retina as in the rest of the central nervous system.

The first point arising in opposition to the hypothesis that vasospasm produces the neural lesions is that the spasms might be a result, and not a cause, of lesions in the nervous system. This possibility is remote. Multiple sclerosis characteristically affects myelinated fibers, and not unmyelinated fibers, such as supply the blood vessels. Secondly, the symptoms affected by the drugs are not like secondary, coincidental phenomena; they are typical symptoms of the disease itself—scotomas, reduction in visual acuity, diplopia and the intention tremor. These facts indicate that the observed phenomena are not secondary to the disease; nor are they coincidental.

The reports of Horton and his co-workers [9] on the beneficial effects of injections of histamine diphosphate in cases of multiple sclerosis will, like claims for any other mode of therapy of this disease, require many years of substantiation before the treatment can be accepted as useful. This effect is quite a separate matter, however, from the transient benefit from histamine diphosphate experienced by some patients while the flush is present. We have observed several patients who could walk more steadily during a flush following the subcutaneous administration of 0.0005 to 0.001 Gm. of histamine diphosphate. These changes in gait were not measured, but merely observed. The observations must be taken with some reservation, since there may always have been a psychologic effect. One patient could see well enough to read only while experiencing the flush; this, however, may have resulted from an effect of histamine diphosphate on the ciliary body.

The hypothesis that the vasospasms cause the lesions in the nervous system is supported in general by a number of facts concerning multiple sclerosis.

A. The scattered, unsystematic distribution of the lesions. This factor, associated with the studies in which he noted thrombi in small vessels suggested a vascular origin to Putnam.[10] It was the same factor and reasoning which led one of us (R. M. B.) to seek something in the blood itself which could affect myelin and to carry out experiments in which evidence of abnormal lipolytic activity was found. Confirmatory evidence was adduced by some observers, while others disputed

9. Horton, B. T.; Wagener, H. P.; Aita, J. A., and Woltman, H. W.: Treatment of Multiple Sclerosis by the Intravenous Administration of Histamine, J. A. M. A. **124**:800 (March 18) 1944.

10. Putnam, T. J.: Lesions of "Encephalomyelitis" and Multiple Sclerosis, J. A. M. A. **108**:1477 (May 1) 1937. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **38**:1 (July) 1937.

it. The evidence presented in this paper favors an origin from the vessels themselves, instead of from their contents, and this evidence appears more direct and cogent than the older evidences, which favored the blood.

B. The suddenness of onset of many attacks of multiple sclerosis. Massive attacks, producing serious incapacity, frequently appear suddenly, as is well known. Less well appreciated is the fact that single, slight symptoms also often occur suddenly; minor as these symptoms are from the standpoint of incapacity, they are nonetheless attacks of multiple sclerosis. These are very common, and the case records of one of us (R. M. B.), made long before these investigations began, contain many examples. We refer to new symptoms, or to sudden recrudescences of old ones which had improved, and not to the daily fluctuations which are common with all symptoms.

C. The brevity of duration of some symptoms. Close questioning of patients with multiple sclerosis often discloses sudden onsets of transient phenomena, which may last no longer than a few minutes. Examples, culled from the old records of one of us (R. M. B.) long antedating these studies, are given.

V. S.: March 15, 1937: The right leg appears to be weak at times, which makes the patient quite unsteady when she walks. This condition seems to come and go; she walks in this unsteady manner and then two hours later is able to walk in a practically normal manner.

Two or three days ago the patient woke up with a slight attack of double vision, which has also appeared and disappeared at different times of the day.

M. J.: Oct. 9, 1940: The patient's vision becomes blurred after eating and remains so about fifteen minutes.

Jan. 16, 1942: A peppery taste at the end of the tongue has occurred two or three times daily in the past three months; this seems to be worse in strong light or on the patient's attempting to read.

A. H.: Sept. 12, 1940: Three or four weeks ago, while carrying two heavy bags, the patient ran to make a train, and his right leg became "like a dead limb." It felt normal again after he had rested on the train. He had experienced this once before, after climbing a mountain.

H. B.: Aug. 4, 1937: There has been a recurrence of a pins and needles sensation in the tips of all the fingers of the left hand; this sensation occasionally travels up the front of the left hand, and sometimes up the arm to the neck.

N. G.: Feb. 17, 1938: After ten minutes of steady walking, the patient has a feeling of tingling in both thighs and in the buttocks, which lasts about five minutes.

J. F.: Jan. 4, 1936: A moving "dart" before the eyes, present for a long time, is sometimes one big spot and sometimes a "veil of spots."

H. A.; April 10, 1936: The patient experienced sudden weakness while pulling an object in a bending position; this lasted fifteen minutes.

In June or July 1932 he had had noted peculiar sensations in the upper teeth on the right side, especially when frightened or excited. This disappeared in about three weeks.

N. S.: Dec. 3, 1937: In October 1937, while in the subway, the patient had an attack of oscillating vision for about an hour.

E. N.: Aug. 5, 1937: The patient first noticed a momentary feeling of numbness and tingling in all the fingers and in both arms as far up as the elbows.

J. U.: July 10, 1942: The patient's vision became blurred after she had been swimming recently.

Sept. 25, 1943: The patient had an episode of double vision for about ten minutes two weeks ago.

The present series includes 7 cases in which sudden onsets of transient symptoms occurred in known circumstances: case A, in which sudden bright light or sudden emotional tension precipitated attacks of blindness in the left eye; case B, in which hot baths brought on "shimmering vision" and scotomas; cases 13 and 14, in which the act of eating, particularly the taking of a hot drink, caused spasms to appear, with increase in visual impairment (not confirmed objectively); case 20, in which the smoking of a cigaret accentuated the intention tremor; case G, in which an intention tremor was also increased with smoking, and case F, in which, according to the history, the patient experienced diminution of vision when under a hot hair dryer (we did not observe this ourselves). In addition, in case 2 and case C the most noticeable, or only, diplopia occurred on arising in the morning. In all but the last 2 cases the symptom disappeared when the precipitating condition changed. In case 2 the diplopia disappeared in two to three hours, and in case C it improved noticeably in a few hours.

In suddenness of onset and brevity of duration these symptoms have a clinical similarity to those in cases of syphilitic endarteritis with transient monoplegia and in occasional cases of cerebral arteriosclerosis with single or repeated attacks of hemiparesis or other consequences which finally become permanent. The similarity suggests that the pathogenesis of the lesions in the central nervous system may be the same—reduction in blood supply.

D. The occasional symptomatic improvement with cessation of smoking. Corroborative, if not supportive, evidence is found in the symptomatic improvement—though never complete relief—which occasional patients note when they stop smoking. This statement by patients is also included in a number of our case records long anteceding the present investigations. The statement coincides with the observations made in case 20 and case G. An autonomic effect on the phenomena of the disease is suggested. The situation (incomplete improvement) may be similar to that of the immediately reversible component of a symptom associated with a fixed component.

Putnam [10] and his associates described thrombi in some of the venules adjacent to the plaque and formulated the hypothesis that the neural lesions may result from the thrombi. It may be that the Putnam hypothesis and the one now presented are closely related. The thrombi

could be secondary to stasis associated with prolonged, intense arteriolar spasm, or to intimal injury when the spasm involves venules. Wagener [8e] suggested that in cases of hypertension thrombosis of retinal vessels may follow injury to the vessel wall as a result of spasm.

ATTACKS AND REMISSIONS

Experimental.—It is necessary to stress the time factor in the experiments with drugs. The transient improvement in function could not have been due to spontaneous remission, for it followed the administration of the drugs immediately and regularly.

"Spontaneous."—It is quite possible that the sudden attacks of scotoma which occurred in some cases were actual attacks of multiple sclerosis if our hypothesis is correct. Many of these attacks had known precipitating causes, it will be remembered.

It would seem possible that many people might have such slight attacks as these at various times of their lives, in which the process is actually that of multiple sclerosis but which are not repeated and which do not result in fixed lesions. Such attacks might never come to the attention of the family physician or the neurologist.

If the hypotheses outlined are correct, two possible types of "spontaneous" remission would appear to be possible in the regular course of multiple sclerosis. One type could result from disappearance of vasospasms which were responsible for disturbances of function without permanent injury to tissue. "Acute remissions" of this type, although transient, appear to have occurred in these experiments. As long as the conditions causing vasospasm persisted, the disturbances of function returned presumably—although this was not demonstrated—as soon as the effect of the drug wore off. Observations many months later in some cases, such as 11 and 12, showed normal retinal vessels and no scotomas or visual impairment.

The other type of remission could follow the healing of actual lesions in the central nervous system. Illustrative observations have been recorded earlier in the paper (i. e., the central scotoma in case 12).

REFLEX ORIGIN OF SOME ATTACKS

The precipitation of sudden attacks of symptoms by light, heat, eating or emotional tension indicates that some of the vessels may become constricted by reflex action. It may be assumed that such vessels must be sensitized in some way for this to occur; presumably, it would not happen to vessels which had not previously undergone constriction for other reasons. There is some evidence that when this occurs it may involve, or at least include, the same vessels repeatedly; in case A it was the left eye alone which was involved again and again, for several years. Yet later the right eye became included as well.

Eliciting of attacks by heat coincides with the report of Simons [11] on the rapid, untoward symptomatic effects of heat in many cases of multiple sclerosis. Exposure to the hot sun may rapidly increase all the symptoms in these cases.

FUTURE PROBLEMS

Additional research is now needed, first, into the cause of the spasms. This is entirely unknown. Allergy suggests itself, but only a few of the patients with spasm were known to have been afflicted with allergy in any form. In 1939 Baer and Sulzberger [12] tested for atopy a group of patients with multiple sclerosis at the Montefiore Hospital and a group under the observation of one of us (R.M.B.). The incidence of atopy was "little higher than that to be expected in any equivalent unselected group studied by the same methods." This does not mean that multiple sclerosis may not be influenced by allergy in a patient who has both conditions. Kennedy [13] described cases in which the disease was clinically indistinguishable from multiple sclerosis and allergy appeared to play a potent role, and we have seen some cases as well. However, no correlation has yet been found between allergy and the vasospasms we have described.

Some observers believe that multiple sclerosis is a syndrome, representing more than one cause. This may be true, and vasospasms may prove to occur in only one group. Further study will be needed to elucidate this point.

Additional symptoms of multiple sclerosis should be studied according to the principles employed in this investigation. Such symptoms should be new, or should have a new component. The symptom should be recordable in some objective way. The observations should be made just before and just after the administration of vasodilating drugs.

THERAPY IN TERMS OF THE HYPOTHESIS

Therapeutic efforts have been commenced on the foundation of these observations. The hypothesis would call for continued vasodilatation of the vessels of the nervous system, as well as for the prevention of spasm. Both these measures should be in force for twenty-four hours a day. A drug-free interval of even a few minutes would suffice for an attack. We have no certain means of maintaining uninterrupted

11. Simons, D. J.: A Note on the Effect of Heat and of Cold upon Certain Symptoms in Multiple Sclerosis, Bull. Neurol. Inst. New York **6**:385, 1937.

12. Baer, R. L., and Sulzberger, M. B.: Role of Allergy in Multiple Sclerosis, Arch. Neurol. & Psychiat. **42**:837 (Nov.) 1939.

13. Kennedy, F.: Allergic Manifestations in the Nervous System, New York State J. Med. **36**:469, 1936.

vasodilatation at present. A far better approach might be employed if the fundamental cause of the spasms could be ascertained.

In the meantime, we have used what resources were available. These include oral administration of papaverine hydrochloride, sometimes in doses as large as 0.045 Gm. every two hours when the patient is awake; aminophylline; belladonna in a dosage sufficient to cause and maintain visual blurring; syntropan, and histamine diphosphate, given according to the method of Horton and his co-workers. Histamine diphosphate has also been given subcutaneously in doses of 0.005 to 0.001 Gm., repeated every fifteen or twenty minutes for three or four doses, in such a way as to maintain a flush for sixty to ninety minutes. This mode of administration, which is simpler than the infusion, was first suggested by a junior member of the house staff of Mount Sinai Hospital, whose identity has been lost. Whisky or wine has also been administered in continuous small doses for several days and nights, in sufficient doses to maintain a feeling of being affected by alcohol. Recently we have employed benadryl and pyribenzamine hydrochloride.

No report can be made as yet on the effect of any of these therapeutic attempts except to say that several patients have regressed while taking benadryl or pyribenzamine. Possibly these drugs may be more helpful to other patients. We have gained only an impression that a combination of syntropan (up to 0.7 Gm. per day) and aminophylline in tolerance doses may be more effective than the other drugs. In cases of multiple sclerosis the spontaneous remissions interfere with the evaluation of treatment, and it is necessary to observe patients for a long time in order to satisfy whatever criteria we use for evaluation. Conclusions should be based not on how many patients improve, but on the incidence of regressions and of new symptoms over a long period.

The possibility of paradoxic reactions should be kept in mind in treating patients according to the hypotheses presented here. Such reactions were observed in case 11. The assumption must be made that fixed lesions in the vessel walls associated with a paradoxic reaction to drugs would be harmful to the patient and that perhaps vasoconstricting drugs should be substituted in such a case. We have seen at least 1 instance in which the patient gave the appearances of doing well on syntropan combined with aminophylline, then suddenly regressed and promptly improved again when administration of the drugs was terminated.

The frequency of precipitation of attack of increased impairment of function by such ordinary events of everyday life as eating and consuming hot drinks suggests that once the vessels are vulnerable to spasm almost anything may produce or accentuate it. One therapeutic indication may be the use of narcosis, with feeding by vein so as to produce as complete freedom from stimuli as possible.

SUMMARY

1. Observations on 18 patients with multiple sclerosis who showed constrictions of some of the retinal arterioles are reported. In 1 case, constriction was seen in a retinal venule. The observations are summarized as follows:

(*a*) The constrictions appeared (1) as isolated areas of narrowing in limited parts of arterioles; (2) in hourglass form, and (3) in segmented form (broken columns of blood were seen in the vessels, with white areas between them). In addition, alternating opening and closing of an arteriole were seen in 3 cases. In 1 instance constrictions kaleidoscopically appeared and disappeared in the whole arteriolar tree while the examination was proceeding. Pulsations of the whole arteriolar tree were seen occasionally.

(*b*) Scotomas were usually associated with the constrictions, and sometimes there was also reduction in visual acuity. The objective findings coincided with the patient's subjective complaints. Some patients complained of a shimmering of the object seen, which caused its outlines to be blurred.

(*c*) In most instances in which they were employed, fast-acting vasodilating drugs caused prompt, temporary reduction of the constrictions and of the size of the scotomas (sometimes to zero). In several instances there was an increase of visual acuity as well.

The drugs used were amyl nitrite, administered by inhalation, and papaverine hydrochloride, administered by vein.

(*d*) In 4 cases with early or transient diplopia, the degree of diplopia was reduced by the inhalation of amyl nitrite.

(*e*) The intention tremor in 2 cases was increased by the smoking of a cigaret. In 1 case, the intravenous injection of papaverine hydrochloride prevented this effect; the imbibing of liquor also prevented it and transiently abolished the basic intention tremor as well.

(*f*) Constrictions and scotomas were both found frequently to be multiple and to shift in position.

2. The constrictions are regarded as spasms.

3. The hypothesis is developed that the lesions throughout the central nervous system in multiple sclerosis are caused by diminution of the blood supply which results from the spasms.

4. Evidence is presented which suggests the existence of two types, or grades, of scotoma and of diplopia—one transient and affected by vasodilating drugs; the other fixed and unaffected by the drugs. The two types may merge and be revealed jointly in one symptom. When the transient part is reduced by the drugs, the fixed part remains.

The hypothesis is proposed that the fixed lesions result from a vasospasm either more complete or of longer duration than the vasospasm responsible for the reducible symptom. The reducible symptom is interpreted as a consequence of transient or incomplete spasm which permits the passage of sufficient blood, promptly or swiftly enough, to preserve the life of the tissue, but which, nonetheless, impairs function; the dilation of the vessel by the drug permits the temporary reestablishment of normal nutritional conditions and the disappearance of the reducible symptom.

5. Attention is called to the frequency of sudden, brief attacks of minor, as well as major, symptoms in multiple sclerosis. In this series, attacks of visual disturbance are recorded as precipitated by heat (hot baths, hot drinks, sitting under a hot air dryer), by eating, by emergence from the dark into strong light and by emotional disturbance. In 2 cases the smoking of a cigaret caused exaggeration of the intention tremor. This evidence suggests that some of the vessels (presumably previously "sensitized" in some way) may become constricted by reflex action.

6. It is pointed out that the transient improvements in function could not have been due to spontaneous remissions, for they followed administration of the drugs immediately and regularly.

It is quite possible that the sudden attacks of scotoma which occurred in some cases were actual attacks of multiple sclerosis. In many of these there were known precipitating causes.

It would seem possible that many people might have such slight attacks as these at various times of their lives, in which the process is actually that of multiple sclerosis but which are not repeated and which do not result in fixed lesions. Such attacks might never come to the attention of the family physician or the neurologist. If the hypotheses outlined are correct, two possible types of "spontaneous" remission would appear to be possible in the regular course of multiple sclerosis. One type could result from disappearance of vasospasms which were responsible for disturbances of function without permanent injury to tissue. "Acute remissions" of this type, although transient, appear to have occurred in these experiments. The other type could follow the healing of actual lesions in the central nervous system.

7. No satisfactory evidence is avilable to explain the vasospasms.

Dr. Harry Van Dyke, professor of pharmacology, Columbia University College of Physicians and Surgeons, contributed advice concerning the use of the drugs and rendered other assistance. Mr. John Sheldon prepared the figures.

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LATE EFFECTS OF INJURY TO THE BRAIN DUE TO SHELL FRAGMENTS AND GUNSHOT

Neurologic and Psychiatric Observations

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THE PURPOSE of this paper is to present observations on the physical and psychologic status of men with penetrating injuries of the brain seen in the late period of recovery. How are these men several months after they were wounded and on their arrival at a general hospital in the United States? How well have they tolerated cerebral injury under modern surgical methods and control of infection? What continuing problems, symptoms and defects do they have at this stage?

Reports on the residual signs of craniocerebral injury often evidence little regard for underlying pathologic or physiologic changes or factors in selection of cases. It was demonstrated by Denny-Brown [1] and emphasized by Lynn and associates [2] that there is a difference in the intracranial alteration produced by trauma of the acceleration-deceleration type, crushing trauma and penetration of missiles. In the first type of trauma diffuse cerebral alteration results; in the other two, focal injury. I believe it is extremely rare that pure focal injury occurs. The laws of physics of penetrating missiles indicate a wide dispersion of energy when the brain is penetrated.[3] The presence and duration of post-traumatic amnesia in cases such as I shall present likewise indicate diffuse cerebral alteration.[1]

The observation of large numbers of cases of craniocerebral injury leads to an awareness of factors of selection. All survivors of severe head wounds are evacuated to a neurologic-neurosurgical center. In the case of the patient with a simple fracture or a minor scalp wound and only brief unconsciousness and amnesia, the story is different. He will

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1. Denny-Brown, D.: Cerebral Concussion, Physiol. Rev. **25**:296-325 (April) 1945.

2. Lynn, J. G.; Levine, K. N., and Hewson, M. A.: Psychological Tests for the Clinical Evaluation of Late Diffuse Organic, Neurotic and Normal Reactions After Closed Head Injury, A. Research Nerv. & Ment. Dis., Proc. (1943) **24**:296-378, 1945.

3. Fulton, J. F., in discussion on Gurdjian, E. S., and Webster, J. E.: Experimental and Clinical Studies on the Mechanism of Head Injury, A. Research Nerv. & Ment. Dis., Proc. (1943) **24**:48-97, 1945.

not be evacuated unless he manifests continued complaint and disability sufficient to warrant release from duty and evacuation. Thus, there may be selection by means of continued complaint. I believe that this factor of selection operates also in reports of many civilian statistics and is often overlooked.

It is with these facts in mind that I present a series of 100 cases. In all instances, wounds were produced by flying, penetrating missiles under conditions of combat, and the dura and the brain were known to be wounded. For the most part, then, selection occurred only so far as the men were selected for army and front line combat duty. Otherwise, it can be assumed that the series studied is a representative cross section of survivors so wounded, for they all had to be evacuated.

MATERIAL

In a series of 320 consecutive admissions of men with head injuries to an army neurologic-neurosurgical center in the zone of the interior, there were 100 cases of open head injury with surgically proved penetration of the dura and injury of the brain due to shell fragments or gunshot. Most of the men arrived at the hospital within six months of their being wounded and remained three to nine months. All were personally examined and observed by me during their entire period of hospitalization.

DATA

Age.—Fifty-one patients were under 25 years of age; 45 were in the age group of 25 to 34 and 4 were 35 or older.

Time Between Injury and Admissions to Hospital.—Thirty-eight men arrived at this hospital less than three months after they were wounded; 40, from three to six months after injury; 18, from seven to twelve months after injury, and four over a year later. Causes of tardy appearance at this center included severe wounds prohibiting evacuation; wounds of parts other than the head, especially orthopedic injuries (which required primary attention), and previous treatment at other neurologic-neurosurgical centers.

Cause of Wound.—In 87 cases the wounds were produced by shell fragments, and in 13, by gunshot.

General Impression of Severity of Injury to Brain.—The final diagnosis set forth on each patient's record required an estimation of the severity of the injury to the brain. Any attempt to quantify injury to the human brain, even when the necropsy specimen is available, is admittedly subject to many criticisms. However, a crude clinical impression was reached in each case, and the designations of mild, moderate or severe injury to the brain were used. It was realized that no clearcut delineations were possible. Injury may be extensive in some portions of the brain and yet betray only mild alteration on clinical observation. Cerebral injury may be actually minor from the

pathologic standpoint but located in such a manner as to produce much observable motor, sensory or psychologic dysfunction. In the previously intellectually dull soldier or in the schizoid patient, the impression may erroneously be reached that profound psychologic alteration ascribable to cerebral damage has occurred. Psychoneurotic and psychoneurotic-like problems arising after head injury may likewise confuse the issue.

In arriving at the clinical estimate, commonly accepted criteria were used, such as the surgeon's data (presence of foreign bodies, degree of penetration, destruction of the brain and meninges, extent and locus of débridement, herniation, fungation and infection); duration of unconsciousness, delirium and amnesia; subsequent complaints and defects; neurologic signs; spinal fluid findings; psychologic performances; clinical course and degree of recovery to date; electroencephalographic disturbances; roentgenographic changes in the skull and, at times, pneumoencephalographic evidence, and knowledge of the patient's previous attainments, personality and background. The integration of these facts was used, rather than any single yardstick or mathematical formula.

1. In 9 cases the diagnosis was mild injury of the brain. The following case is illustrative of this group:

A private aged 20 was wounded five months prior to arriving at this hospital by fragments of a high explosive shell which struck the right preauricular region, penetrating the right temporal squamosa at the base of the skull, the right maxillary sinus and the right mandibular joint. He recalled being struck and became unconscious for an unknown period; he was then delirious and amnesic for three days. The surgeon's report indicated a laceration of the dura and a small shell fragment immediately beneath it. No further tract was observed. A small herniation followed initial débridement but cleared spontaneously. The only neurologic signs recorded indicated partial paralysis of the right third nerve, which likewise disappeared. Recovery was otherwise uneventful except for a great number of complaints and right maxillary sinusitis, which responded to puncture of the antrum. On arrival at this hospital, the patient complained of right-sided headaches, excessive nervousness and constipation. Social service investigation, psychologic testing and psychiatric study of the patient revealed serious preexisting psychoneurotic difficulties. Intellectual loss due to damage to the brain could not be demonstrated. The electroencephalographic tracing was normal. Neurologic examination revealed only hypesthesia over the first two divisions of the right fifth cranial nerve.

2. In 61 cases the diagnosis was moderate injury to the brain. The following case is a common example of this group:

A 23 year old corporal was wounded by shell fragments low in the right occipitoparietal region five months prior to entry to the hospital. The laceration of the scalp was approximately 6 cm. long. A large defect in the skull, measuring approximately 8 cm. in length and 4 cm. in width, was the result of operation. Many fragments of bone were removed from a tract at least 2 cm. deep. The

patient did not recall being struck, was unconscious for several days and had no recollection of the ten days following the day on which he was wounded. Hernia cerebri with moderate infection developed but subsequently disappeared. He was bedridden one month. On arrival at this hospital, he complained of visual loss and awkwardness of the left arm and leg. A roentgenogram revealed a large defect in the skull with radiating fracture lines extending into the floor of the middle fossa. Neurologic examination revealed left homonymous hemianopsia; the left pupil was larger than the right; both pupils reacted poorly to light; there were slight hemiparesis and astereognosis on the left side and anosmia on the right. Careful psychologic investigation indicated intellectual defects, which, however, did not appear to be immediately disabling. The electroencephalographic tracing disclosed only a generalized distribution of borderline slow waves.

3. In 30 cases the patient was considered to have suffered severe injury to the brain. A typical example follows.

A 20 year old private was wounded by shell fragments six months prior to entry to this hospital. He was struck in the right occipital region, the missiles penetrating the left frontal region and producing a large tract with small foreign bodies throughout. Initial roentgenograms revealed that the largest foreign body would roll back and forth in the tract as his head was turned from side to side. He also incurred a compound, comminuted fracture of the radius of the right arm and severe lacerations of that arm. He did not recall being struck, was unconscious six days and remained delirious and amnesic for the ensuing six weeks. Signs of decerebrate rigidity were present during this time. Recovery was stormy. On arrival at this hospital he was bedridden and triplegic and demonstrated complete left homonymous hemianopsia and cortical sensory loss over the entire left side of his body. He confabulated somewhat, although he was correctly oriented. He was unstable emotionally and became enraged easily. His electroencephalographic tracing revealed a focus of very slow waves in the right occipital region. Social service investigation disclosed that in civilian life he had had average intelligence. One year after he was wounded samples of his intellectual performance indicated abilities in the mental age range below 13 years.

Other Details Concerning the Wounds.—Penetration deeper than 2 cm. into the brain tissue was ascertained in 60 cases from surgeons' notes and the presence of foreign bodies. Accompanying hematomas (subdural or intracerebral) were described in 10 cases. Evidence of infection complicating recovery was found in 26 instances. In 10 cases cerebral hernia was reported. In 2 cases there was full blown meningitis (eventually controlled by chemotherapy). Localized and superficial infection was the most common type of infection reported. In 2 cases there was definite evidence of extradural abscess. Osteomyelitis of the skull was a complication in 4 cases, in 3 of which several renewals of tantalum plates were required. The number of cases of infection after arrival at this hospital was small and diminished as the war progressed. It appeared as time went on that patients were evacuated less rapidly to the zone of the interior, for which reason more time and energy could be devoted to the clearing up of infections. In 15 cases infection was present on the patient's arrival here. In 4,

it was primarily chronic, localized osteomyelitis of the skull; in the remaining cases it consisted of chronic superficial infection in the scar site, involving the brain (locally) in 6 instances. Recurrent meningitis occurred in 1 case but was adequately controlled with chemotherapy.

Site of the Wound.—In 30 cases the frontal bone was primarily involved and in 30 others the occipital bone. In the rest of the cases the injury was classified loosely as parietal. In 16 cases the wound was located in the vertex and extended across the midline. In 3 cases the injury was classified as multiple, the wounds having been incurred at several cranial sites simultaneously.

Presence of Other Wounds.—In 37 cases wounds were incurred elsewhere than in the head. In 13 cases these wounds were of major proportion, with the following distribution: fracture of a large, long bone and multiple soft tissue wounds, 5 cases; fracture of more than one large, long bone, 2 cases; fracture of only one large, long bone, 2 cases; abdominal and visceral perforations, 3 cases; perforation of the chest with pneumohemothorax, 1 case. The presence of these wounds could not be shown to have any effect on recovery from the cerebral injury. There was no clinical reason to suspect fat or air embolism in these cases.

Recall.—Of 80 cases in which information on the point was obtainable, the patient recalled having been struck by the shell fragments or having received the gunshot wound in 50 (62 per cent). Of the remaining 30 (38 per cent), 10 (12 per cent) had a retrograde amnesia, in addition to amnesia for the injury. There was every indication that men who could not recall being struck were more severely wounded.

Duration of Unconsciousness.—From the records of 62 men an estimate of the state of consciousness following injury was possible. Of these 62 patients, 13 (21 per cent) apparently were not unconscious at any time. This was ascertained from the patient's statements, as well as from field medical records. Eleven (18 per cent) were unconscious less than fifteen minutes. Concerning the remainder, estimations became exceedingly difficult because the cessation of "unconsciousness" was vaguely defined. Maintenance of records under conditions of combat was of necessity difficult. Some patients evidently became unconscious repeatedly, so that a second or a third period of unconsciousness would have to be considered. Operative procedures, anesthesia and preoperative and postoperative sedation often confused these estimations. Of the men rendered unconscious, it was ascertained that approximately one-third were not immediately rendered so.

Duration of Post-Traumatic Amnesia.—Discussion of the anamnesis with the patient and a careful review of his records provided a reason-

able estimate of the duration of amnesia following his wound. My colleagues and I endeavored to adhere to strict criteria in defining amnesia.[4] The subjective experiences of being "dazed," "in a fog" or "forgetful" which the patient recalled at the time of treatment were not considered significant. Of 73 cases in which data were obtained, there was a history of post-traumatic amnesia of less than twenty-four hours' duration or none at all in 18 (25 per cent). In 16 per cent it lasted one to three days; in 29 per cent, four to seven days; in 8 per cent, eight to fourteen days; in 8 per cent, fifteen to twenty-one days, and in 14 per cent, over twenty-one days. Prolonged amnesia was found to be correlated with the presence of definite neurologic signs, amnesia for the wound incident, "organic facies" and intellectual loss. It cannot be overlooked that operative procedures, anesthesia, sedation, infection and dehydration likewise contributed to the production of prolonged amnesia. However, the exact role that these factors played could not be ascertained in this group of men, who had been treated under combat conditions.

Chief Complaint on Entry.—Headache was the commonest complaint, appearing in 39 cases. However, in only 9 cases was it severe enough to cause the patient routinely to seek rest or medication. In 15 instances distress was primarily at the site of the wound, and in 18 others it was in that general quadrant. In 2 cases distress was localized to the wounded side of the head, and in 4 others, to the opposite side. In 6 cases sharp, jabbing pains in the scalp were described. In 18 cases continued attenuation of distress was admitted. A survey of precipitating and aggravating factors (by means of a standard questionnaire concerning one hundred conditions) revealed that during hospitalization headaches were most commonly precipitated and aggravated by visual strain and emotional reactions. Jarring, exertion, train rides and positions in which the head is low were also incriminated, but less prominently.

In 33 cases the patient complained of visual disturbances. Destruction of the geniculocalcarine pathways or the calcarine cortex was at fault in 26 cases. In 6 instances one eye was damaged (in addition to destruction of the geniculocalcarine pathway in 2 cases, so that the patient had only partial vision in the remaining eye). In 3 other cases visual loss was due primarily to destruction of the optic nerve fibers in or anterior to the chiasm.

In 52 cases motor disability in one or more extremities was complained of. In 18 instances this amounted to complete hemiplegia; in 7 others, to triplegia or paraplegia, due to midline involvement of the paracentral lobule.

4. Psychological Terms Used in Cases of Head Injury, Medical Research Council, Great Britain, Brit. M. J. **1**:525 (April 5) 1941. Russell, W. R.: Accidental Head Injuries: Prognosis in Service Patients, Lancet **1**:7-10 (Jan. 2) 1943.

Language dyspraxia and dysgnosia ("aphasias") were present in 20 cases. The commonest overt disabilities concerned expression in speech and writing.

Dizziness (not true vertigo) was a complaint in 9 cases; tinnitus, in 8 cases, and deafness, in 9 cases. Anxiety symptoms, such as tension, hyperhidrosis, combat dreams, insomnia, nervous trembling and palpitation, were complained of in 11 cases, but in only 4 cases could they be considered moderately severe. In 4 cases frequently recurrent convulsive episodes comprised an important complaint. Diplopia was present in 5 cases and anosmia in 6 cases. In 1 case there was complete paralysis of the facial nerve (peripheral type). In 6 cases intellectual defects were complained of, although in other cases of such defects the patient appeared to lack insight thereof on arrival. In 8 cases there was no complaint whatever.

Gross Estimation of Disability on Arrival.—Disability was graded on the over-all impression of mental and physical incapacity. The patient who was bedridden or wheelchair-ridden, requiring assistance to eat, dress and attend to his toilet, was graded as severely disabled. So was the occasional man with so great an intellectual loss that his performance was now considered at or below the borderline of mental deficiency. Thirty of the 100 patients appeared to merit classification as severely disabled.

A moderately disabled soldier could get around on crutches or with a cane and had at least a dull normal retention of general intellectual assets. Twenty-eight men were regarded as belonging to this category.

The typical mildly disabled man had paresis of one or two limbs, hemianopsia or mild "aphasia." Twenty-four men were in this category.

The patient with only subjective disability presented no objective signs or deficits (other than defects of the skull). There were 14 such patients. Four men exhibited no complaints, objective signs or disability (other than defects of the skull).

Defects of the Skull.—On arrival at this hospital, all the men had defects of the skull. Many, if not most, of these defects were of the magnitude encountered as a result of débridement. It appeared that the size of the defect had more to do with the surgeon's discretion and habits than with the severity of the injury. Estimation in terms of square centimeters of area revealed defects of 2 to 10 sq. cm. in 46 cases, of 11 to 20 sq. cm. in 29 cases and of greater than 20 sq. cm. in 25 cases. In addition to these defects, radiating fracture lines were demonstrated in 32 cases. The presence of fracture lines radiating from these defects correlated significantly with indicators of severe damage to the brain.

Other Complicating Factors in Convalescence.—In 12 cases convalescence was complicated by a prisoner of war status, acute appendicitis,

malaria, severe frostbite, trench foot, postoperative pulmonary infarcts or abscess, hypertension, acute hepatitis due to infection and intestinal parasites. None of these complications, however, could be shown to be deleterious in the recovery of the men from their cerebral injury.

Neurologic Findings.—The cases were divided into three groups on the basis of the neurologic findings: (1) no neurologic changes, in 9 cases; (2) minimal, scattered or nonlocalizing signs, in 20 cases, and (3) definite localizing neurologic signs, in 71 cases. In 58 cases of the last group the signs were of "motor" type (indicating plegia, paresis or manual dyspraxia). In 2 cases the disability was paraplegic, and in 5 it was triplegic. In 6 other cases, however, disability consisted in minimal paresis. In 26 cases lesions were demonstrated in the geniculocalcarine pathway or the calcarine cortex which resulted in defects in the visual fields. Residual evidences of language dyspraxia and dysgnosia ("aphasias") were present in at least 20 cases. From the records available, such disturbances had existed previously in at least 13 additional cases but were no longer detectable by clinical and psychologic tests after the patient's arrival at this hospital. Of the 20 cases with residual signs of dyspraxia and dysgnosia on arrival here, the disturbances were of relatively minor character in 9. In only 2 of the remaining 11 cases could the defects be considered severe, and in but 4 cases was strenuous reeducation for "aphasia" required. In the remaining 7 cases the aphasia cleared up remarkably with general intellectual stimulation.[5] It is recalled here that in 48 cases of this series wounds had been received in the dominant hemisphere.

Astereognosis (usually associated with plegia or paresis) was found in 38 cases. Signs referable to the cerebellar tract were present in 5 cases (in 3 of which they were ascribable to direct involvement of the cerebellum). Clinical evidence of contrecoup injury could be established presumptively in only 5 cases—in 3 by neurologic signs, in 1 by the electroencephalographic tracing and in 1 by ventricular distortion in the pneumoencephalogram.

The cranial nerves were partially or completely involved as follows: olfactory nerve, 10 cases; third cranial nerve (including its nuclei), 9 cases; fourth and sixth cranial nerves, 1 case each; fifth cranial nerve, 4 cases; seventh cranial nerve, 1 case of peripheral and 14 cases of central lesion; eighth cranial nerve, 4 cases (excluding cases of deafness due to other causes, including blast injury), and twelfth cranial nerve (paresis), 7 cases. Anisocoria was found in 18 cases; in 8 cases the larger pupil was on the same side as the site of injury.

Diabetes insipidus from damage to the pituitary-hypothalamic complex was present in 1 case.

5. Aita, J. A.: Men with Brain Damage, Am. J. Psychiat. **103**:205-213 (Sept.) 1946.

In 29 cases the facies was characteristic of organic lesions. It consisted of a dull, washed-out, poorly expressive facial display. Expressions were slow to appear and disappear; they were listless, erratic, childlike, occasionally parkinsonian (masked, staring or immobile; 4 cases) or reminiscent of hepatolenticular degeneration (Wilson's disease) (fatuous, vacant facies, punctuated with sudden mechanical changes of expression, often stereotyped, such as a spastic grin; 3 cases). These findings were found to correlate significantly with severe cerebral injury and disability, deep penetration of the foreign body and prolonged delirium and amnesia, especially if the patient was not of prior dull normal intelligence.

Sensation of electric shock on flexion of the neck was present in 4 cases. This symptom is taken as an indication of concomitant injury to the spinal cord.[6]

Convulsive Seizures.—These had occurred at least once since the day of injury in 25 cases. In but 1 case was there uncertainty as to the nature of the disturbance, and in this instance the clinical picture of syncope (vasomotor?) was deemed a more likely diagnosis. In 8 cases convulsive seizures appeared within five months of the wound. In the remaining 17 cases seizures started later. Most of the men had only one to four seizures, at intervals of one to three months, which were easily controlled by medication. In 4 cases, however, seizures were more frequent and decidedly a major complaint, not easily managed by medication alone. In only 6 cases were jacksonian characteristics demonstrated.

Personality Change.—It was my repeated impression that the patient's present reactions and "personality" were not due to intracranial alteration alone. Personality phenomena which followed injury arose from both the personality of the wounded man and his now altered brain. Specific cases may serve as illustrations.

CASE 1.—Palpitation, morning vomiting and apprehension during convalescence. A study of the previous personality revealed that a pronounced sense of insecurity had been a lifelong trait, with enuresis up to the age of 15, nail biting and frequent nightmares prior to army service.

CASE 2.—Difficulty in rehabilitation despite average intelligence. When confronted with his irresponsible attitude toward rehabilitation, the patient complained of inability to decide what he would like to do. He frequently shirked classes and expressed multiple complaints and excuses. Social service investigation revealed

6. Allen, I. M.: Immediate and Remote Effects of Minor Lesions of the Cervical Portion of the Spinal Cord Following Head Injury, Australian & New Zealand J. Surg. **10**:157-172 (Oct.) 1940. Walshe, F. M. R.: Commonly Unrecognized Type of Injury to the Cervical Spine and Spinal Cord in Association with Head Injuries, Lancet **2**:173-175 (Aug. 5) 1944. Bender, M. B., and Furlow, L. T.: Sensations of Electric Shock on Flexion of Neck as a Sign of Head Injury, J. Neurosurg. **3**:212-217 (May) 1946.

that the patient had been reared in meager socioeconomic circumstances and a turbulent family setting. He left home while quite young, did not get along with any member of his family and held no job longer than four weeks.

CASE 3.—Pronounced apathy and listlessness despite good intelligence ratings. The patient was constantly listless, uninterested and mildly depressed. He preferred to complain about his various disabilities, including complete paralysis of the right seventh cranial nerve. If left alone, he would sit, occasionally reading or listening to the radio. Discussion with his family revealed that he had always been apathetic, that he had to be "pushed" and could not decide (in the four years following graduation from high school) what he wanted to do. Sibling competition had left him drably passive and dependent.

CASE 4.—Lack of interest in rehabilitation. The patient, vociferous, enthusiastic and good natured, was found to be uninterested in any attempt to rehabilitate himself physically or psychologically. Discussion with his family revealed that he had been constantly unemployed in the interval between leaving school and entering the Army (a five year period), and he had always talked about getting a job but never had one. He had always been known for "tall tales," frequently telling people that he signed a contract to play for a famous national baseball team, when actually he was playing only local semiprofessional baseball. His occasional amusing confabulations during hospitalization were said by his family to be little different from those he habitually produced in civilian life.

CASE 5.—General irresponsibility, gambling, squandering and nomadism. A follow-up of the patient, who had a severe injury to the right frontal lobe, revealed that he was not working and that he was living a nomadic existence, gambled freely and was involved in minor illegal activities. Investigation of his background revealed that he had been reared by an aged aunt and uncle, toward whom he rebelled early in life, and that his present existence was but an exaggeration of the way he had lived prior to military service.

CASE 6.—Suspected personality changes due to frontal lobe deficit. The patient was noted for his excessive jocularity, irresponsibility, alertness and facetiousness. He amused every one with excellent repartee. At first it was readily assumed that he was suffering from a frontal lobe deficit. However, even after several furloughs home his family could see but little change from the personality they always had known.

In addition, several patients with schizoid reactions (1, to be described, had an actual psychotic episode) were found by social service investigation to have always had these outstanding trends.

Red Cross social service research, psychologic tests (the Wechsler-Bellevue scale,[7] the Rorschach test[8] and the Minnesota Multiphasic

7. Wechsler, D.: The Measurement of Adult Intelligence, ed. 3, Baltimore, Williams & Wilkins Company, 1944, p. 258.

8. (*a*) Armitage, S. G., and Reitan, R. M.: A Critical Evaluation of Certain Psychological Measures, Including a Proposed Screening Test for Determination and Evaluation of Brain Injury, to be published. (*b*) Klopfer, B., and Kelley, D. M.: The Rorschach Technique, New York, World Book Company, 1942. (*c*) Aita, J. A.; Reitan, R. M., and Ruth, J. M.: Rorschach's Test as a Diagnostic Aid in Brain Injury, Am. J. Psychiat., to be published.

Personality Inventory [9]), psychiatric interviews and long term acquaintance with the patients during recovery and rehabilitation indicated changes in personality in 53 cases. Associated with severe cerebral injury and intellectual loss was the personality picture of the passive, listless, dull, apathetic soldier (10 cases). Euphoria, irresponsibility and poor judgment were outstanding in 6 other cases, although associated with direct wounds of the frontal lobe in only 3 cases. Except for certain intellectual deficits, few personality changes could be blamed primarily on cerebral damage, and many were ordinary, run-of-the-mill reactions of men who had experienced the army, combat and wounds. Of course, the patients with previous outstanding personality liabilities were in no way improved with cerebral injury and its experience. During hospitalization the incidence of psychoneurotic reactions was low, there being only 4 men who demonstrated a severe anxiety state (due for the most part to combat experiences). One other patient had complete flaccid paralysis of an upper extremity, which responded well to hypnosis. Three severely wounded men were noted for reactive irritability and temper outbursts, but they manifested a great drive for rehabilitation. In only 2 patients did a reactive depression appear (due primarily to incapacity), and in both the response to psychotherapy was good. Another soldier exhibited a schizophrenic-like psychosis after the covering of a defect in the skull with a tantalum plate. (There was no infection; the patient was well oriented, and of superior intelligence; he was involved in aloof, paranoid preoccupations and demonstrated inappropriate, facetious affect.) This condition disappeared in a few weeks except for residual schizoid signs. Four men became very dependent on hospital care and increasingly insecure about discharge. They devised numerous minor excuses and complaints to forestall their release. Only 1 patient was suspected of malingering (with the goal of receiving more compensation). Disciplinary problems were rare in this group of men, with many months of hospitalization. Only 1 man of the group was absent without leave; 1 became intoxicated frequently, and 1 was caught in naïve, readily discovered stealing. This record was in sharp contrast to that of the disciplinary problems repeatedly arising in other wards in this hospital where wounded men were undergoing treatment.

In only 25 cases did the men admit dreaming two to four times a week. Combat experiences were relived occasionally in 9 cases and frequently in 3 cases. One did not get the impression that these men had a great deal of nervousness due to combat experiences. Reasons for this scarcity of neurotic symptoms may be many. These patients

9. Hathaway, S. R., and McKinley, J. C.: The Minnesota Multiphasic Personality Inventory, Minneapolis, University of Minnesota Press, 1943, p. 16.

were an unselected group of wounded men, representing a cross section of all soldiers who fulfilled requirements for combat duty. It may be significant, also, that since they were wounded and were cared for as wounded men there was no biologic need to react with other symptoms. Their medical disposition was settled. Our laboratory aids, such as the Rorschach test and the Minnesota Multiphasic Personality Inventory, revealed significant neurotic responses in only one third of these men. (Indications of anxiety, depression and hypochondriasis were common in this group.)

The problems concerning most of these men were practical and concrete. What work could they do? What education could be sought? What pension would be obtained? Would the pension be decreased if they rehabilitated themselves and returned to work? What would be the ultimate effects of the wound? Would seizures develop? Would insanity, blood clots, hemorrhages, paralysis or cerebral tumor occur later? Would pneumoencephalographic studies or further neurosurgical procedures be necessary?

In a few instances, marital difficulties and family illnesses presented problems. Several men expressed much concern that they would be a burden on an already crowded home when they returned.

Estimation of Prior Intelligence.—On the basis of previous educational attainments, work records, social responsibilities, earnings, military skills and clues furnished by the present psychologic tests and by persons acquainted with him, each man was categorized according to his most likely prior intelligence level. Twenty-four men were rated as having superior intelligence (mental age estimated as over 18 years); 54 were considered of average intelligence (including high average and dull average ranges), and 22 of borderline defective intelligence (mental age under 12 years). Theoretically, the army sent no morons into combat.

Intellectual Losses.—It is reasonable to theorize that almost every patient included here lost some intellectual assets by his wound. In the more severely injured, deficits were evident to even the untrained observer. Yet among the men who suffered minor and probable discrete or superficial cortical damage, no intellectual losses could be diagnosed.

How could these deficits be estimated? We have found the following investigations helpful:

1. Psychologic study with the Rorschach test, the Wechsler-Bellevue test and methods suggested by Goldstein [10] and others.[11] These tests

10. Goldstein, K.: After Effects of Brain Injuries in War, New York, Grune & Stratton, Inc., 1942.

11. Armitage and Reitan.[8a] Aita and others.[8c]

give clues as to prior and present performances, as well as to specific types of deficit often seen among persons with injury to the brain.

2. Social service investigation regarding the previous personality, educational attainments, social responsibilities, earnings, work record and changes now apparent to persons who had been closely acquainted with the patient for many years.

3. Clinical interviews with the patient; examination of his stream of thought, thinking difficulties and judgment.

4. Observation of the patient while on an active rehabilitation program by persons skilled in detecting intellectual difficulties.[5]

Allowance was always made for physical incapacities (such as deafness, aphasia, hemianopsia or hemiplegia) which might hinder performance on the more psychologic aspects of testing.

As physicians, we were concerned with one practical question concerning disability. Had this man's loss of intellectual assets been sufficient that it should be included in the official diagnosis, which would ultimately entitle him to veterans' compensation on the basis of post-traumatic encephalopathy, manifested by loss of intellectual assets?

In only 37 cases were deficits sufficiently impressive to require such a label. In 18 cases these deficits were striking. Clinical determination indicated that 14 men with previously superior intelligence had now slipped into the average range. Eleven men with previous average intelligence were now of borderline defective to defective intelligence. Twelve men with previously borderline defective intelligence were believed to have lost further assets (although this was the most difficult group to evaluate). On the basis of severe intellectual defects, custodial care was considered for 5 patients. Such care was actually found necessary for only 1 patient; the other 4 had excellent home settings and understanding families.

Severe intellectual losses were found in 8 of the 30 men with occipital wounds, whereas only 2 of the 30 men with frontal wounds demonstrated such severe deficits. (Posterior injuries often result in additional contrecoup contusion of the frontal lobes.[12])

More interesting were the specific intellectual deficits demonstrated. The intellectual assets of men with these injur s are not devastated en masse, to reduce them to a more or less feebleminded" level.[13]

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12. Courville, C. B.: Contre-Coup Mechanism of Craniocerebral Injuries, Arch. Surg. **45**:40-53 (July) 1942.

13. Goldstein, K.: The Significance of Mental Disturbance in Rehabilitation of Soldiers with Brain Injury, Tr. Am. Neurol. A. **70**:22-24, 1944; The Problem of Cerebral Localization from a Clinical Point of View, in Halloran, R. D., and Yakovlev, P. I.: Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Waltham, Mass., Metropolitan State Hospital, 1942, p. 530, lecture 14. Footnote 10.

Rather, deterioration, whether great or slight, is uneven and selects certain intellectual assets, permitting others to remain remarkably preserved. The deficits and distress of these men cannot be understood unless these spotty defects are known.

Patient, family, employer and physician alike may be unaware of specific intellectual deficits because retention of other assets permits covering up or substitution. These men with intellectual losses frequently retain previously accumulated factual data, the common information of everyday adult life, vocabulary and verbal abilities, old memories, habits and concepts previously learned and the ability to handle readily meaningful or concrete concepts. They can often manage the problems immediately at hand, especially if these can be dealt with unreflectively. They frequently use trial and error methods successfully, without detection by persons untrained in recognizing their deficits. In addition to demonstrating these intellectual retentions and adjustments, performances reveal dogged perseverance and perfectionism, strict adherence to directions and retention of social amenities—all of which may be very disarming.

Psychologic tests [8a] of intellectual components revealed loss of ability to analyze and synthesize. These patients were unable to change their method of attack on problems or to shift attitudes or concepts. Memory defects were manifest for recent occurrences. The men lacked anticipation, organization and planning ability. They were unable to deal comprehensively with variables, more than one aspect of a problem or dual relationships. It was difficult for them to handle new problems, especially those not depending on old information and habits. Attention and concentration were impaired, being especially sensitive to anxiety. Their thinking often showed evidences of helpless repetitiousness and stereotypy, or actual perseveration. They tried doggedly, often recognizing some inadequacy, but were helpless to change their attack.

Electroencephalographic Tracings.—Records were declared normal in only 10 cases. In 52 cases they were borderline normal [14] including records of generalized moderately slow and moderately fast activity. In 38 cases the records were classified as showing abnormal, very slow, very fast or focal (or spiking) activity. In 23 cases records of focal activity were obtained. Asymmetry of amplitude was present in the records of 75 men. The majority of electroencephalographic abnormalities were found in the records of patients most recently wounded.

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14. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification, Arch. Neurol. & Psychiat. **50**:111-128 (Aug.) 1943. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Company, 1941. Electroencephalography: Operative Technique and Interpretation, United States War Department Technical Bulletin (TB Med. 74) Washington, D. C., Government Printing Office, July 27, 1944.

Besides the initial records described in the preceding paragraph, three serial records were obtained in 62 cases over an average period of six months. Although in 54 cases tantalum plates were inserted at one time during the study we could not prove that this procedure affected the electroencephalographic tracings subsequently obtained. In 18 cases (30 per cent) definite improvement occurred in the record, and in 8 cases (13 per cent) a greater degree of abnormality appeared. Asymmetry of amplitude appeared later in one third of the records which did not demonstrate it initially. It remained in one half of the records in which it appeared initially. These facts could not be correlated with available clinical data.

Course of Physical Disability.—On arrival at this hospital, 9 men were bed patients. On discharge, 5 of these were actively ambulatory, 3 of whom required a cane. The remaining 4 were triplegic with persisting paraplegia requiring dependence on wheelchairs. On arrival here, 14 others entered as wheelchair patients. All these men became actively ambulatory before their discharge, 5 of whom continued to require a cane. Fourteen men (out of this total of 23) had a useless upper extremity on discharge.

Continued disability could not be accounted for merely on the basis of the severity and location of the injury as such. Neither could it be fully understood by mere knowledge of the presence of convulsions or hemiplegia. Bare neuropathologic or neurophysiologic summaries of what the injury had produced left much to be desired. Only when the patient concerned was studied could the entire picture of disability be comprehended.

Prognosis.—On the patient's discharge from this hospital, each case record bore a prognosis. This was ascertained primarily from the standpoint of practical employability. It did not consider unpredictable seizures. In 7 instances the prognosis was "poor," predicting a lifetime of total incapacity—wheelchair existence, mental impairment and inability to care for more than simple needs.

In 30 cases the prognosis on discharge was "fair." In these cases there was physical and/or mental impairment, but part time or simple occupational adjustment warranted anticipation.

In 46 cases the prognosis was rated as "good." These men suffered only minor impairments and/or subjective symptoms. It was anticipated that they could not attain previous levels of work efficiency but they should be able to work full time.

In 17 cases the prognosis was "excellent" because the men had inconsequential impairment (barring the future development of convulsions), and tentatively they were considered "as good as before."

Rehabilitation in the Hospital.—This has been described in detail elsewhere.[5] It included a carefully integrated and individualized program designed to assist each man to relearn and to compensate for and circumvent his defects.

Dispositions.—Eighty-three men were given medical discharges directly from this hospital. Six others were transferred first to a convalescent center and subsequently given medical discharges. Seven men were sent to other specialty centers (ophthalmology or otology or plastic surgery). Only 4 patients were transferred directly to a veterans' hospital. With 3 of these men this transfer was necessary primarily because of severe physical handicaps; with the other, because of intellectual impairment, euphoria, irresponsibility and insufficient assets and understanding at home to assist in continued rehabilitation. It appeared evident to all medical officers who saw these patients at disposition boards that the men with a prognosis of "excellent" could have been returned to duty, and many of those rated as "good" could likewise have continued to serve in a limited capacity.

SUMMMARY

The recent war has brought numbers of young, healthy men with severe alteration of intracranial structures, who, for the first time in history, will live and somehow adjust because modern neurosurgical skill and control of infection have allowed them to. These young men will be with us for many years, and their problems of distress, deficit, disability and pension will be encountered repeatedly not only by the specialist but by the general practitioner as well.

I have described observations in a representative cross section of men with penetrating injuries of the brain during the late phase of recovery. Unlike men with the post-traumatic syndrome (following closed head injury or concussion), who were usually evacuated only on the basis of continued complaints, all these men were evacuated because of the location and nature of their wounds. Hence, we saw a cross section of all soldiers so wounded.

Findings were presented in detail, and from these the general plan of study and evaluation of each patient was evident. On his admission, the immediate problem concerned what had happened to him. He and his previous medical records were searched for clues. This information, together with neurologic examination and laboratory technics, permitted a diagnosis of the alterations which were present, their location, severity and course to date. Neurosurgical considerations were constantly required.

The patient who had the injury and consequent disabilities was scrutinized. Who was he before this injury? Personality characteristics, family setting, life experiences, attainments and anxieties comprised

part of the biologic material now altered. Combat, the wound, long hospitalization, treatment and convalescence, family and the future presented a constant stream of problems and anxieties. What had he left with which to continue life? His brain was altered, and he must go on variously, with motor defects, sensory distortions, convulsive seizures, loss of intellectual assets, headaches, dizziness or emotional instability. His was a struggle for adjustment to these confusing handicaps.

At the stage of recovery described, he had not encountered or experienced fully the range of complexity of his defects.

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PSYCHOPHARMACOLOGIC STUDY OF SCHIZOPHRENIA AND DEPRESSIONS

III. Lactic and Pyruvic Acid Content of the Blood Before and After Administration of Sodium Amytal

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IT HAS been reported [1] that patients with schizophrenia or depression differ from each other in their clinical and psychologic responses to the intravenous administration of subnarcotic doses of sodium amytal followed by amphetamine sulfate N. N. R. One such prominent difference is in the development of tolerance to these drugs in terms of the type and duration of the psychologic response, which developed rapidly in patients with schizophrenia but more slowly in patients with depression.

Since barbiturates inhibit, in vitro, the oxidation of *d*-glucose, lactate and pyruvate in brain tissue,[2] may not the explanation of the differences in the responses of these two groups of patients to sodium amytal lie in differences of oxidation of carbohydrate? Looney [3] reported that there is a relatively greater accumulation of unoxidized lactic acid in the blood of schizophrenic patients than in the blood of normal subjects as a response to graded exercise. He and Childs,[4] moreover,

From the Iowa State Psychopathic Hospital and the Departments of Pharmacology (Dr. Featherstone and Mr. Carter) and Psychiatry (Dr. Gottlieb), State University of Iowa College of Medicine.

1. Gottlieb, J. S., and Coburn, F. E.: Psychopharmacologic Study of Schizophrenia and Depressions: I. Intravenous Administration of Sodium Amytal and Amphetamine Sulfate Separately and in Various Combinations, Arch. Neurol. & Psychiat. **51**:260 (March) 1944. Gottlieb, J. S.; Krouse, H., and Freidinger, A. W.: Psychopharmacologic Study of Schizophrenia and Depressions: II. Comparison of Tolerance to Sodium Amytal and Amphetamine Sulfate, ibid. **54**:372 (Nov.-Dec.) 1945.

2. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. **19**:135 (April) 1939.

3. Looney, J. M.: Changes in Lactic Acid, p_H, and Gases Produced in the Blood of Normal and Schizophrenic Subjects by Exercise, Am. J. M. Sc. **198**:57 (July) 1939.

4. Looney, J. M., and Childs, H. M.: The Lactic Acid and Glutathione Content of the Blood of Schizophrenic Patients, J. Clin. Investigation **13**:963 (Nov.) 1934.

indicated that there is an inverse relation between the amount of lactic acid in the blood and that of glutathione, a substance which is, or acts as, a coenzyme, in schizophrenic patients but not in normal controls. Stotz and Bessey,[5] however, reported that the lactate: pyruvate ratio for patients with depression and schizophrenia did not differ significantly from that of normal subjects.

More recently, in general metabolic studies greater emphasis has been placed on pyruvate metabolism both in isolated tissues and in the intact organism. Stotz and Bessey [5] and Friedemann and Haugen [6] have advocated the use of the blood lactate: pyruvate ratio to distinguish true abnormalities of pyruvate metabolism from difficultly controlled fluctuations furthered by such factors as anoxia, exercise and food consumption.

The present study, therefore, was designed to answer the questions: Does the lactic or the pyruvic acid content of venous blood or their ratio differ among groups of patients with depression or schizophrenia and of normal subjects? Does the intravenous administration of sodium amytal produce differences in either lactic or pyruvic acid or their ratio in these three clinical groups?

METHOD

Determinations of the lactic and pyruvic acid contents of venous blood were obtained on 15 patients with depression, 12 patients with schizophrenia and 12 normal controls. Both before and one-half hour after the standard intravenous administration of 250 mg. of sodium amytal followed by 20 mg. of amphetamine sulfate N. N. R.,[7] determinations of the amounts of lactic and pyruvic acids were obtained on 9 patients with depression, 8 patients with schizophrenia and 3 normal subjects. All patients and control subjects were in a basal state: complete rest in bed and no food for the preceding twelve hours. For each determination a sample of 5 cc. of venous blood was collected in a chilled 10 cc. syringe and was propelled through the needle into 5 volumes of cold 10 per cent trichloracetic acid within forty-five seconds of the time of the withdrawal of the first cubic centimeter. The method of Friedemann and Haugen [6] was used for the quantitative determination of pyruvic acid and that of Barker and Summerson [8] for lactic acid. All determinations were made in duplicate and within three hours after the second withdrawal of the blood.

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5. Stotz, E., and Bessey, O. A.: The Blood Lactate-Pyruvate Relation and Its Use in Experimental Thiamine Deficiency in Pigeons, J. Biol. Chem. **143**:625 (May) 1942.

6. Friedemann, T. E., and Haugen, G. E.: Pyruvic Acid: I. Collection of Blood for the Determination of Pyruvic and Lactic Acid, J. Biol. Chem. **144**:67 (June) 1942; II. The Determination of Keto Acids in Blood and Urine, ibid. **147**:415 (Feb.) 1943.

7. Amphetamine sulfate prepared for intravenous administration was supplied by the Smith, Kline & French Laboratories, Philadelphia.

8. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535 (April) 1941.

RESULTS

The results of the analyses of the blood for lactic and pyruvic acids and their ratios, before and after the intravenous administration of sodium amytal, are shown in the accompanying table.

The lactic: pyruvic ratios for the groups of patients and for the normal controls before sodium amytal was given were compared for significance by the use of Fischer's t [9]: depressed versus schizophrenic patients, $t = 0.320$; depressed patients versus normal subjects, $t = 0.120$; schizophrenic patients versus normal subjects, $t = 0.430$. These values are in agreement with those of Stotz and Bessey,[5] who found that the lactate pyruvate ratios for depressed and schizophrenic patients did not differ significantly from the ratio found for normal subjects.

Lactic and Pyruvic Acids and Their Ratio for Normal Controls and for Patients with Either Depression or Schizophrenia Before and After Intravenous Administration of 250 Mg. of Sodium Amytal *

	Number of Subjects	Lactic Acid, Mg./100 Cc.	Pyruvic Acid, Mg./100 Cc.	Ratio Lactic Acid : Pyruvic Acid
Before sodium amytal				
Normal controls.....	12	6.85 ± 0.64	0.975	7.04 ± 0.86
Depressed patients.....	15	8.45 ± 1.14	1.170	7.23 ± 0.93
Schizophrenic patients	12	8.00 ± 0.98	1.050	7.63 ± 0.82
After sodium amytal				
Normal controls.....	3	8.07	0.920	8.61 ± 1.27
Depressed patients.....	9	8.40	1.220	6.92 ± 0.42
Schizophrenic patients	8	8.65	0.980	8.89 ± 1.12

* Values are given as means or as means and standard errors.

Our values for lactic acid, however, were considerably lower than theirs, probably owing to the difference in methods used and the fact that our patients were kept under basal conditions.

The absolute values for lactic acid of the blood before administration of the sodium amytal were lower for the normal controls than for either group of patients, but the t values (depressed versus schizophrenic patients, $t = 0.318$; depressed patients versus normal subjects, $t = 1.300$; schizophrenic patients versus normal subjects, $t = 0.982$) indicate that these differences were not significant ones.

Values for the lactate: pyruvate ratio before and after administration of sodium amytal for each group of patients were not significantly changed (before and after administration of sodium amytal for depressed patients, $t = 0.304$; before and after administration of sodium amytal for schizophrenic patients, $t = 0.422$; before and after administration of sodium amytal for normal controls, $t = 1.027$).

9. Values for Fisher's t greater than 2.0 are significant.

COMMENT AND CONCLUSIONS

From these data, it would appear that the lactic and the pyruvic acid contents of venous blood and their ratio do not differ significantly for patients with either depression or schizophrenia from the values for normal controls under basal conditions. The data, furthermore, suggest that the intravenous administration of sodium amytal in a dosage of 250 mg. is not sufficient to change significantly any of these values. This experimental approach does not assist, therefore, in the elucidation of the differential response of the two groups of patients to this drug.

Although there is no essential difference in the general condition of the oxidative reactions as so determined among the two groups of patients and the normal controls, the possibility of other metabolic disturbances is not eliminated. The data simply suggest that general metabolic disturbances may be sought either before or after the pyruvate: lactate phase in the carbohydrate oxidation-reduction system. Neither is the possibility of more specific metabolic disturbances in the central nervous system eliminated. For such studies, blood should be obtained from both the carotid artery and the jugular vein.

The values for the lactic acid of the blood here reported are lower than those recorded elsewhere in the literature, probably as the result both of the method used and of the basal state of the subjects.

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THE ELECTROENCEPHALOGRAM IN ENCEPHALITIS

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CURIOUSLY little has been written about the electroencephalographic changes found in association with encephalitis. A report of 1 case was published by Lindsley and Cutts,[1] and the "Atlas of Electroencephalography" [2] contains figures and several references to this subject. A more extensive report was published by Ross,[3] but it was based on only 4 cases. Since encephalitis is a clinical condition of major importance, and since some of the most definite abnormalities that are seen in electroencephalography are encountered in patients with this condition, it seems appropriate to report on a larger number of cases.

MATERIAL AND METHOD

This investigation is based on 240 cases of a disorder clinically diagnosed as encephalitis, studied in different phases of the disease. Ideally it would be desirable to base such a survey on longitudinal data and on electroencephalograms prior to infection; but, for obvious reasons, this is exceedingly difficult if not impossible. Ideal conditions have been only roughly approximated by combining longitudinal and cross sectional data and by assuming that the patient's electroencephalogram prior to infection was normal. Twenty-seven cases were studied during the acute phase of the disease, and repeat electroencephalograms were obtained in the subsequent subacute phase in 8 of these. Twenty-five additional cases were studied in the subacute phase, to bring the total in the subacute group to 33. Electroencephalograms were obtained in 180 cases in the postacute phase; 5 of these were cases in the subacute group in which repeat studies were made. The various etiologic factors represented in the series are shown in table 1, as well as the phases in

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1. Lindsley, D. B., and Cutts, K. K.: Clinical and Electroencephalographic Changes in Child During Recovery from Encephalitis, Arch. Neurol. & Psychiat. **45**:156-161 (Jan.) 1941.

2. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings, 1941.

3. Ross, I. S.: Electroencephalographic Findings During and After Acute Encephalitis and Meningoencephalitis, J. Nerv. & Ment. Dis. **102**:172-182 (Aug.) 1945.

which the studies were made. The age distribution of the patients in the postacute phase is shown in table 2. Electroencephalograms were recorded on a six channel Grass electroencephalograph with monopolar leads from the frontal, parietal, occipital and temporal areas. The indifferent lead was formed by interconnected electrodes on both ear lobes.

RESULTS

In the 27 cases in which the electroencephalogram was obtained in the acute phase of the encephalitis (table 1), slow waves of very

TABLE 1.—*Diseases Acting as Etiologic Factor in 240 Cases of Encephalitis*

Etiologic Disease or Agent	Acute Stage, No. of Cases	Subacute Stage, No. of Cases	Postacute Stage, No. of Cases
Undetermined	10	11 (3*)	91 (2 †)
Influenza	11	11 (3*)	35 (1 ‡)
Measles	3	2 (1*)	14
Whooping cough	0	0	9
Pneumonia	2	4 (1*)	10 (1 †)
Mumps	0	1	3 (1 †)
Scarlet fever	0	0	6
Osteomyelitis	1	0	3
Typhoid	0	1	1
Mastoiditis	0	0	2
Smallpox vaccine	0	1	0
Herpes	0	0	1
Rheumatic fever	0	1	1
Diphtheria vaccine	0	0	1
Botulism	0	0	1
Sinusitis	0	1	0
Chickenpox	0	0	1
Otitis media	0	0	1
Total number	27	33 (8*)	180 (4 †)(1 ‡)

* Patients studied in acute and subacute stages.
† Patients studied in subacute and postacute stages.
‡ Patients studied in acute through postacute stage.

TABLE 2.—*Age Distribution in 180 Cases of Encephalitis in Postacute Phase*

	Age, Yr.						
	0-5	6-10	11-15	16-20	21-30	31-40	41+
With seizures	29	16	15	13	12	6	5
Without seizures	5	7	7	10	28	16	11

high voltage were apparent. Examples of this type of activity are shown in figures 1 and 2. The slowing was in some cases focal, in others generalized. If the clinical disorder increased in severity, the electroencephalogram became more abnormal, showing still higher voltage and slower waves. In 33 cases studied in the subacute phase (table 1) the electroencephalogram tended to be less abnormal, with

scattered slow waves and with much interposed normal activity (figs. 1 and 2). In cases without seizures the electroencephalogram tended to return to normal during the postacute phase (figs. 1 and 5). However, in some cases, as illustrated in figure 2, it remained slightly abnormal after the patient was free of symptoms (fig. 2).

In the cases in which clinically evident seizures developed in either the subacute or the postacute phase the electroencephalogram was likely to show interseizure discharges of the same type as are commonly

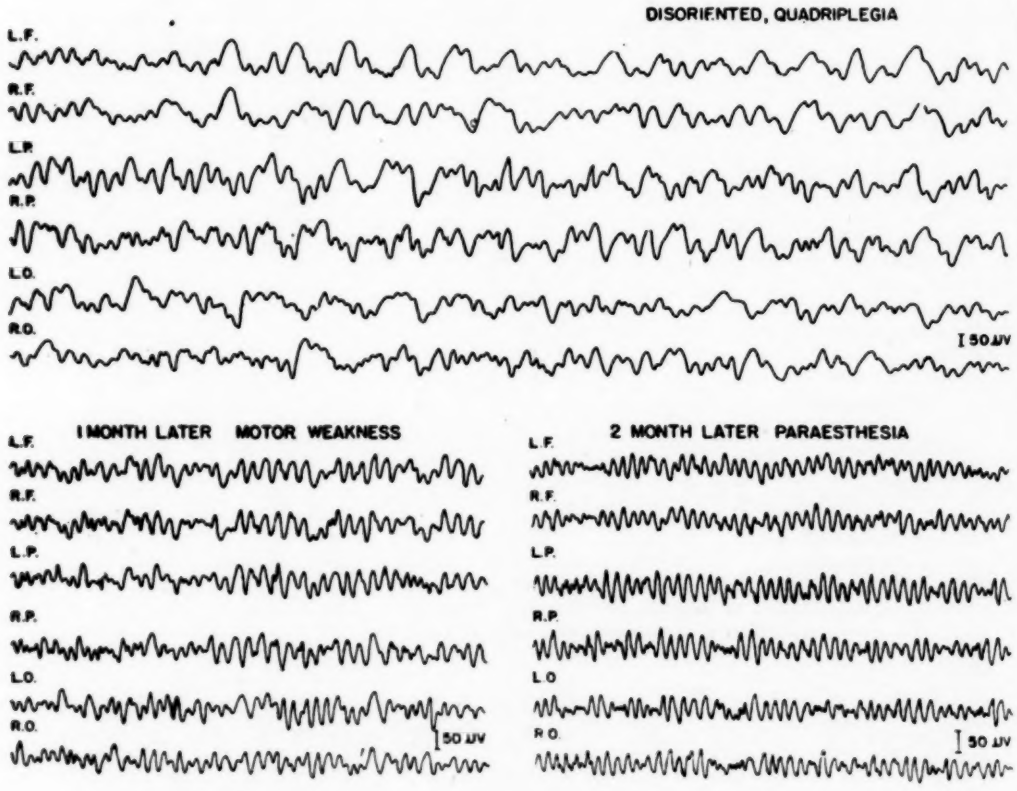

Fig. 1.—Electroencephalograms in a patient aged 42 with encephalitis complicating influenza.

encountered in immediate association with clinical seizures (fig. 3). Three per second activity of the classic petit mal type was common. It was of interest to attempt to determine whether any difference exists between the interseizure electroencephalograms of patients with convulsions and of those without convulsions. In figure 4 the entire series was divided into two groups: cases in which clinical seizures occurred and cases in which clinical seizures did not occur. These groups were

further subdivided according to the electroencephalographic classification. During the acute phase there was no electroencephalographic difference between the two clinical groups. During the postencephalitic phase the electroencephalograms in the cases in which seizures did not occur were normal for the most part, the exceptions being only those in which the electroencephalograms showed slightly slow activity. Only 1 per cent of those in the postencephalitic phase without epilepsy had seizure discharges; yet this group was far from asymptomatic. Some had

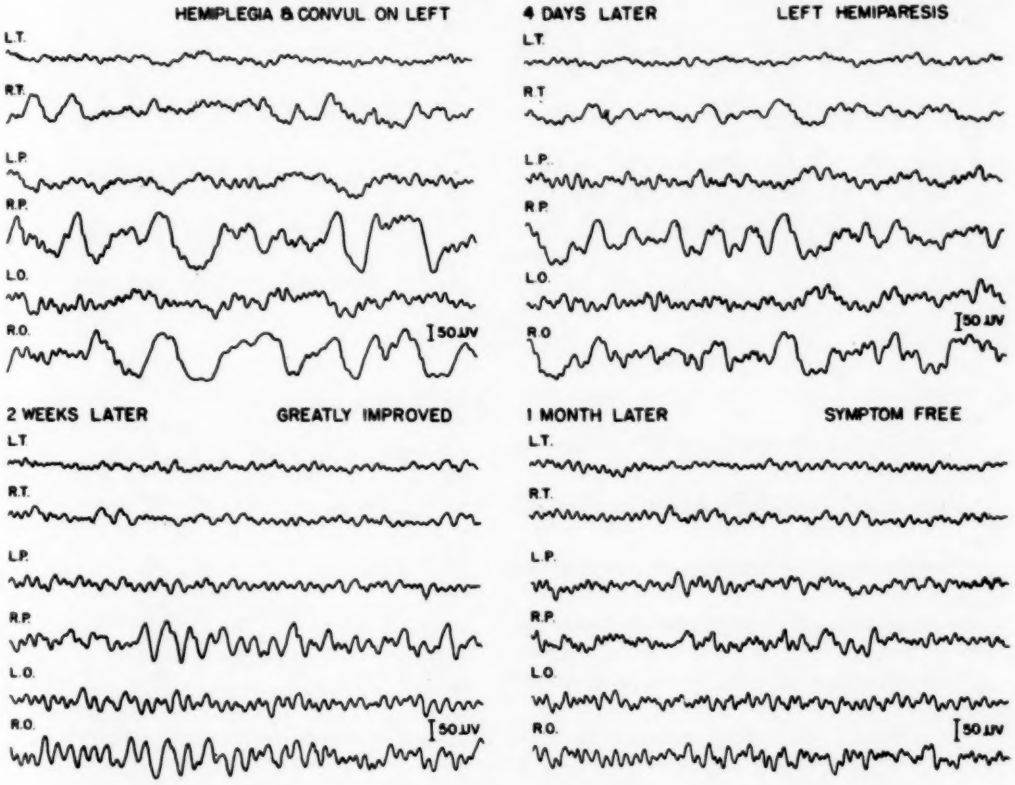

Fig. 2.—Electroencephalograms at various stages of encephalitis in a child aged 10.

paralysis agitans, while others had such symptoms as oculogyric crises and narcolepsy (table 3). Their electroencephalograms, nevertheless, tended to be normal. On the other hand, 58 per cent in the postencephalitic phase with epilepsy had paroxysmal electroencephalograms, i. e., manifest seizure discharges (fig. 3). Thus, only those patients in the postencephalitic phase who had seizures showed a high incidence of electroencephalographic abnormalities.

It would appear from the present data that convulsions are a much commoner postencephalitic symptom in children than in adults (table 2). This observation is in accord with general experience that increasing age gives increasing protection against seizures. As will be seen from table 4, the incidence of focal electroencephalographic abnormality is much higher in the present series of cases of postencephalitic epilepsy than in a group of cases of undifferentiated epilepsy.[4] In this

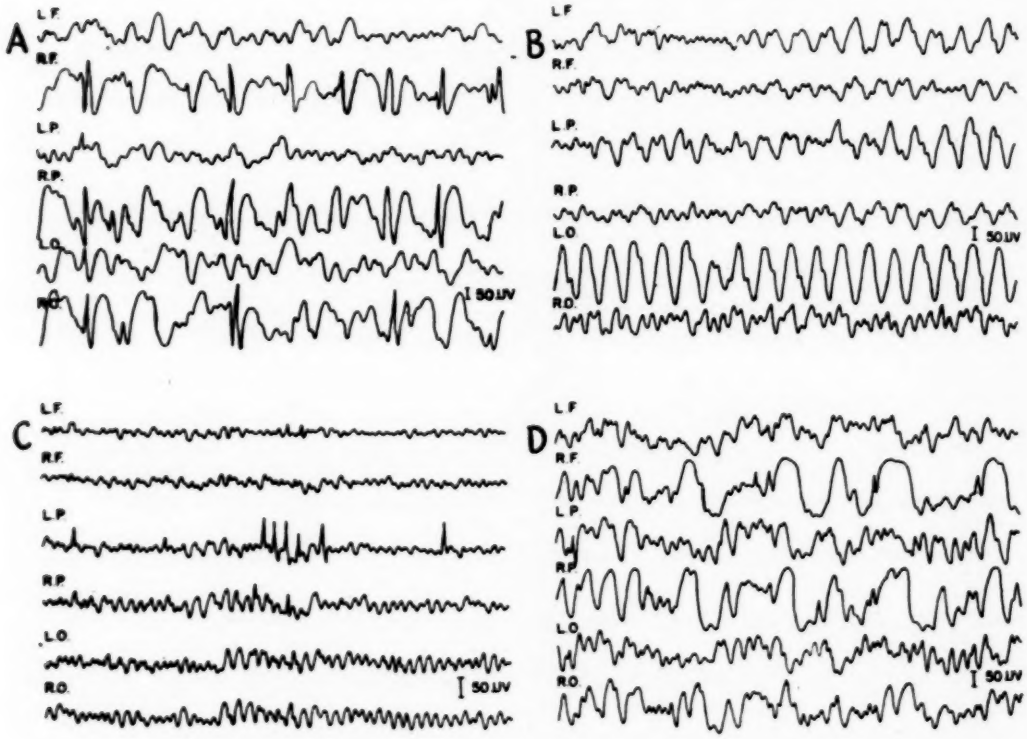

Fig. 3.—Electroencephalograms in 4 cases of postencephalitis with clinical seizures, showing interseizure discharges similar to discharges during seizures. *A*, child aged 4 years, with grand mal and petit mal seizures complicating encephalitis which followed measles; *B*, child aged 9, with grand mal and petit mal seizures complicating encephalitis which followed whooping cough; *C*, child aged 10, with jacksonian seizures occurring during encephalitis following influenza; *D*, child aged 14, with encephalitis of undetermined origin, with grand mal and focal signs.

subgroup of cases of postencephalitis with seizures focal electroencephalographic abnormalities are commoner than focal neurologic signs.

4. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50**:111-128 (Aug.) 1943.

Examples of electroencephalographic foci in cases of postencephalitic epilepsy are shown in figure 3.

COMMENT

Figures 4 and 5 show that in the subacute and postacute phases of encephalitis the electroencephalogram can be given prognostic significance. The situation is much like that found with severe head

TABLE 3.—*Symptomatic Classification of Cases in Postacute Stage of Encephalitis Without Seizures*

Symptom	No. of Cases
Narcolepsy	24
Narcolepsy and cataplexy	14
Paralysis agitans	17
Oculogyric crises	3
Dizzy spells	3
Behavior disorder	7
Paresthesia	3
No symptom	3
Weakness of arm or leg	2
Unilateral paralysis agitans	2
Restlessness	1
Sleep walking	1
Strabismus	1
Mental impairment	1
Dysarthria	1
Headaches	1

TABLE 4.—*Percentages of Focal Encephalographic Abnormality and Focal Neurologic Signs for Patients with Postencephalitic Epilepsy Compared with Percentages for Patients with Undifferentiated Epilepsy*

Clinical Group	Focal Electroencephalogram	Focal Neurologic Signs
Postencephalitic epilepsy (96)	65%	45%
Undifferentiated epilepsy (1,000)	14%	9%

injury,[5] in which practically all patients show abnormal electroencephalograms but with the passage of time the electroencephalograms of those who are not going to have seizures tend to return to normal, whereas the electroencephalograms of those who are going to have seizures either remain abnormal or after slight improvement become increasingly abnormal. That the same statement holds for encephalitis is indicated in figure 5, in which the incidence of very abnormal electroencephalograms (paroxysmal, very slow or very fast) in the

5. Gibbs, F. A.; Wegner, W. R., and Gibbs, E. L.: The Electroencephalogram in Post-Traumatic Epilepsy, Am. J. Psychiat. **100**:738-749 (May) 1944.

groups with and without seizures is plotted against the time course of the disease.

From figures 4 and 5 certain diagnostic and prognostic interpretations are possible; for example, if the electroencephalogram is found

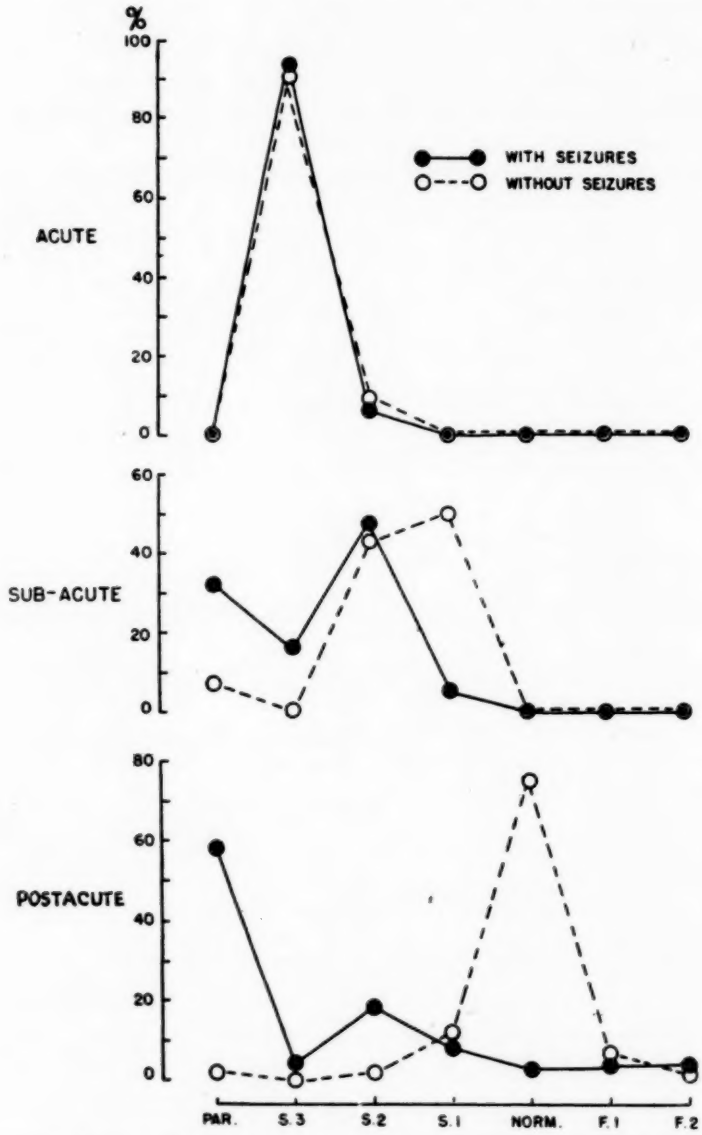

Fig. 4.—Incidence of abnormal electroencephalograms in 240 cases of encephalitis in various phases, divided on the basis of the occurrence of seizures and on the electroencephalographic classification.

to be normal or slightly abnormal during what is supposed to be the acute or the subacute phase of encephalitis, the question should arise

as to whether the clinical diagnosis is correct, for a normal electroencephalogram was never found during the acute or subacute phase in cases of this series and in the great majority of cases it was exceedingly abnormal. In patients with multiple sclerosis who present symptoms suggesting acute encephalitis the electroencephalogram is commonly normal.[6] A paroxysmal or exceedingly slow electroencephalogram (S-3) after the acute phase is over creates a presumption that the patient will have convulsions and raises a question of the desirability of starting anticonvulsant medication to prevent this development. In the subacute phase a slightly slow electroencephalogram carries a good prognosis for the nonoccurrence of convulsions.

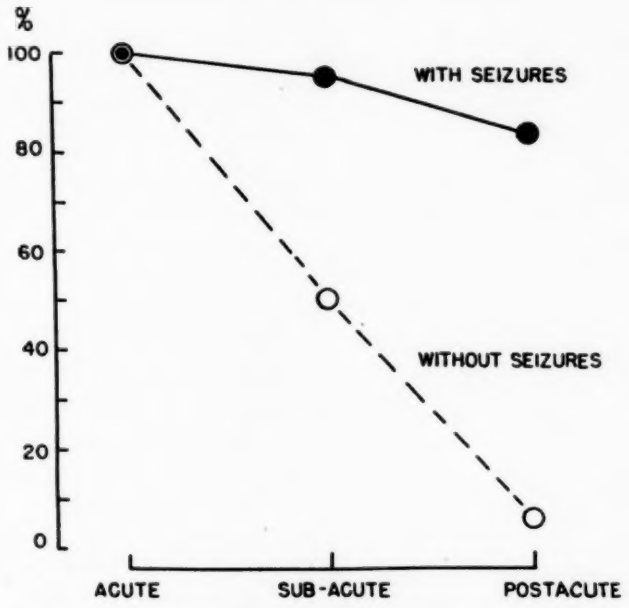

Fig. 5.—Incidence of abnormal electroencephalograms plotted against the phase of the disease for patients with convulsions and those without convulsions.

The high incidence of discharges of the petit mal type in patients with postencephalitic epilepsy contrasts with the rarity of such discharges in cases of epilepsy resulting from birth injury.[7] This difference might result from a difference in the nature of the injury or its location.

6. Hoefer, P. F. A., and Guttman, S. A.: The Electroencephalogram in Multiple Sclerosis, Tr. Am. Neurol. A. **70**:70-73, 1944.

7. Perlstein, M.; Gibbs, E. L., and Gibbs, F. A.: Electroencephalogram in Cerebral Palsy, A. Research Nerv. & Ment. Dis., Proc. (1946), to be published.

SUMMARY AND CONCLUSIONS

The electroencephalograms in 240 cases of encephalitis were studied in various stages of the disease. It was found that abnormality is often focal and that it correlates with the stage of the disease. During the acute and subacute phases it correlates with the general severity of symptoms. However, the only feature of the postencephalitic syndrome which correlates highly with electroencephalographic abnormality is the presence of convulsions.

The electroencephalogram has diagnostic value for encephalitis, and after the acute phase is past it has prognostic value for postencephalitic epilepsy.

Wave and spike activity of the petit mal type is a common sequel of encephalitis in children.

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EFFECT OF ELECTRICALLY INDUCED CONVULSIONS ON PERIPHERAL VENOUS PRESSURE IN MAN

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NEITHER the mechanisms underlying the beneficial effects of electric shock therapy nor the factors responsible for some of the untoward results of that procedure are well understood. Pronounced changes in the physiology of the body as a whole occur during convulsions, and it is therefore important to study them. A recent report by Silfverskiöld and Åmark [1] described changes in venous pressure during electrically induced convulsions in man. It seemed desirable to make a further analysis of the changes observed, and the present report records the results of such a study.

MATERIAL AND METHODS

Fifty-five determinations were made on 12 patients, who ranged in age from 18 to 59 years; 11 subjects were women. The direct method of Moritz and von Tabora [2] was used. A no. 18 or 19 gage needle was inserted into an antecubital vein, and readings were taken until a base line was reached, usually in two or five minutes. The convulsion was then induced; during and after the convulsion the arm used for the measurements was kept extended by means of manual restraint applied well below the point of insertion of the needle. In only 2 of the 55 experiments was the needle dislodged from the lumen of the vein during the convulsion. Readings were made every fifteen seconds after the electric shock and were discontinued when a base line was reached or, in a few cases, when the patient went into a state of postconvulsive excitement.

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1. Silfverskiöld, B. P., and Åmark, C.: Disturbance of Circulation in Convulsions of the Epileptic Type: II. Arterial and Venous Pressure During Electroshock, Acta med. Scandinav. **113**:191, 1943.

2. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

OBSERVATIONS

The initial values for venous pressure lay between 0 and 13 cm. of water and averaged 5.7 cm.; only 4 of the 55 readings were above 10 cm. of water.

During the convulsive seizure the antecubital venous pressure rose to between 35 and 87 cm. of water; in 3 instances the rise was to less than 50 cm., and in 6 it was above 80 cm. The average rise was 63 cm., or 57 cm. above the average control level. The rise reached its maximum during the first fifteen seconds after the shock in 23 instances, reaching in these cases levels of 45 to 85 cm., the average being 60 cm. In the remaining 32 instances the maximal rise during the convulsion was reached thirty or forty-five seconds after the administration of the electric shock. In these instances rises of 1 to 58 cm. occurred after the first fifteen seconds; only 2 of these increases were more than 20 cm., however; and the average for all was only 12 cm.

After the maximal increase in venous pressure was reached during the convulsion, a subsequent decrease occurred in 30 instances while the seizure continued. The decreases ranged from 3 to 44 cm. and averaged 17 cm. of water.

After the end of the convulsion the venous pressure fell rapidly in all but 4 experiments; in 3 of the latter slight rises of 2, 7 and 1 cm. occurred, and in the fourth an immediate fall of only 1 cm. was noted. In all these instances the resumption of respiration was delayed, and when the usual postconvulsive hyperventilation began the venous pressure fell promptly. The return to a base line at a low level of venous pressure occurred within sixty to ninety seconds after the induction of electric shock, or thirty to sixty seconds after the end of the convulsion itself. The control level, however, was reached in only 1 experiment. In all the other experiments the final venous pressure reading was between 4 and 41 cm. above the control level; in only 5 of these, however, was the final level more than 20 cm. above the control level and in these the patients became somewhat excited after the seizure. The final level was, on the average, 13 cm. above the control reading.

COMMENT

Many observers have described elevation of peripheral venous pressure during exercise or straining,[3] the amount varying with the severity

3. (*a*) Moritz and von Tabora.[2] (*b*) Burton-Opitz, R.: Muscular Contraction and the Venous Blood Flow: Venous Pressures, Am. J. Physiol. **9**:161 and 198, 1903. (*c*) Sewall, H.: Experiments on Venous Blood Pressure and Its Relation to Arterial Blood Pressure in Man, J. A. M. A. **47**:1279 (Oct. 20) 1906. (*d*) Hooker, D. R.: The Effect of Exercise on the Venous Pressure, Am. J. Physiol. **28**:235, 1911. (*e*) Schott, E.: Die Erhöhung des Druckes im venösen System bei Anstreng-

(Footnote continued on next page)

of muscular effort. It is of especial interest that several studies have shown that the Valsalva maneuver raises the venous pressure notably, i. e., to levels as high as 50 cm. of water.[4] Much, or most, of the rise in venous pressure observed in the present study was probably a consequence of violent muscular contractions forcing blood rapidly into the

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ung, als Mass für die Funktionstüchtigkeit des menschlichen Herzens, Deutsches Arch. f. klin. Med. **108**:537, 1912. (*f*) Schneider, E. C.: The Circulation of the Blood in Man at High Altitudes: III. The Effects of Physical Exertion on the Pulse Rate, Arterial and Venous Pressure, Am. J. Physiol. **40**:380, 1916. (*g*) Bürger, M.: Ueber die klinische Bedeutung des Valsalvaschen Versuchs, München. med. Wchnschr. **68**:1066, 1921. (*h*) Kroetz, C.: Die Koeffizienten des klinisch messbaren Venedrucks, Deutsches Arch. f. klin. Med. **139**:325, 1922. (*i*) Villaret, M.; St. Girons, F., and Grellety-Bosviel, D.: La tension veineuse périphérique et ses modifications pathologiques, Presse méd. **31**:318, 1923. (*j*) Bedford, D. E., and Wright, S.: Observations on Venous Pressure in Normal Individuals, Lancet **2**:106, 1924. (*k*) White, H. L.: Circulatory Responses to Exercise in Man and Their Bearing on the Question of Diastolic Heart Tone, Am. J. Physiol. **69**:411, 1924. (*l*) White, H. L.; Barker, P. S., and Allen, D. S.: Venous Pressure Responses to Exercise in Patients with Heart Disease, Am. Heart J. **1**:160, 1925. (*m*) White, H. L., and Moore, R. M.: Circulatory Response to Static and Dynamic Exercises, Am. J. Physiol. **73**:636, 1925. (*n*) Meyer, O. O., and Middleton, W. S.: The Influence of Respiration on Venous Pressure, J. Clin. Investigation **8**:1, 1929. (*o*) Bürger, M.: Kreislauffunktionsprüfungen im Sport, Med. Welt **4**:1639, 1930. (*p*) Tornquist, H.: Physiologische und klinische Studien über den Armvenendruck, Ztschr. f. d. ges. exper. Med. **81**:227, 1932. (*q*) Nordenfeldt, O.: Studien über Valsalvas Versuch in seiner Anwendung als "Bürgers Pressdruckprobe," Acta med. Scandinav. **82**:465, 1934. (*r*) Hoffmann, H., and Baumann, H.: Fortlaufende Venendruckmessungen bei Kreislaufbelastung durch den Valsalva'schen Versuch, Ztschr. f. Kreislaufforsch. **26**:729, 1934. (*s*) Baumann, H.: Fortlaufende Registrierung des Venendruckes mittels einer Photozelle, Klin. Wchnschr. **14**:306, 1935. (*t*) Méan, H.: Influence de divers agents, notamment de l'acide carbonique, sur la tonicité des veines périphériques de l'homme, Arch. internat. de physiol. **40**:429, 1935. (*u*) Schneider, E. C., and Collins, R.: Venous Pressure Responses to Exercise, Am. J. Physiol. **121**:574, 1938. (*v*) Liedholm, K.: Studien über das Verhalten des Venendruckes beim Valsalvaschen Versuch, Acta med. Scandinav., 1939, supp. 106, p. 1. (*w*) Nieuwenhuizen, C. L. C: Der venöse Blutdruck nach Arbeitsleistung, eine Funktionsprüfung der Zirkulation, ibid. **103**:171, 1940. (*x*) Szekely, P.: Venous Pressure Responses to Exercise, Am. Heart J. **22**:360, 1941. (*y*) Hamilton, W. F.; Woodbury, R. A., and Harper, H. T., Jr.: Arterial, Cerebrospinal and Venous Pressures in Man During Cough and Strain, Am. J. Physiol. **141**:42, 1944. (*z*) Chapman, E. M., and Linton, R. R.: Mode of Production of Pulmonary Emboli, J. A. M. A. **129**:196 (Sept. 15) 1945. (*a'*) Winsor, T., and Burch, G. E.: Use of the Phlebomanometer: Normal Venous Pressure Values and a Study of Certain Clinical Aspects of Venous Hypertension in Man, Am. Heart J. **31**:387, 1946.

4. Moritz and von Tabora.[2] Bürger.[3g] Kroetz.[3h] Bedford and Wright.[3j] Meyer and Middleton.[3n] Bürger.[3o] Tornquist.[3p] Nordenfeldt.[3q] Hoffmann and Baumann.[3r] Baumann.[3s] Méan.[3t] Liedholm.[3v] Hamilton and others.[3y] Chapman and Linton.[3z] Winsor and Burch.[3a']

veins. Variations in the amount of rise in venous pressure in the same patient at various times are consequent to differences in the violence of the seizure and also to differences in the respiratory level at which the seizure commenced; the maximal intrapulmonary pressure developed during forced expiration depends on the volume of air in the lungs at the beginning of such expiration.[5] During the seizure the patients are apneic, and the violent contractions of the abdominal and thoracic musculature which have been shown to occur during the seizure [6] induce a Valsalva phenomenon. Additional evidence as to the nature of the respiratory changes is the fact that variations in blood pressure during electrically induced convulsions [1] resemble closely those of the Valsalva experiment.[3v] Other factors probably operate. For instance, the changes in blood gases which occur during electrically induced convulsions must also result in elevation of venous pressure. Although asphyxia and anoxia have minor, or inconstant, effects on pressure in the venous system,[7] increase in the carbon dioxide of the blood elevates it [8]; the rise in carbon dioxide tension of blood during convulsions is appreciable.[9] Still other mechanisms favoring elevation of venous pressure may be activated by changes in autonomic function which occur during electrically induced convulsions. Patients in such seizures show evidence of increased sympathetic activity, consisting in pallor and piloerection, and it is possible that increased amounts of epinephrine are present in the body at this time. The fact that epinephrine con-

5. Rahn, H.; Otis, A. B.; Chadwick, L. E., and Fenn, W. O.: The Pressure-Volume Diagram of the Thorax and Lung, Am. J. Physiol. **146**:161, 1946. Silfverskiöld and Åmark.[1]

6. Gordh, T., and Silfverskiöld, B. P.: Disturbance of Circulation in Convulsions of the Epileptic Type: I. Intrathoracic and Intra-Abdominal Pressure During Electroshock, Acta med. Scandinav. **113**:183, 1943.

7. (*a*) Roy, C. S., and Sherrington, C. S.: On the Regulation of the Blood Supply to the Brain, J. Physiol. **11**:85, 1890. (*b*) Plumier, L.: Etude expérimentale des variations de la pression veineuse, Arch. internat. de physiol. **8**:1, 1909. (*c*) Hooker, D. R.: The Veno-Pressor Mechanism, Am. J. Physiol. **46**:591, 1918. (*d*) Schneider, E. C., and Truesdell, D.: The Circulatory Responses of Man to Anoxemia, ibid. **71**:90, 1924. (*e*) Eyster, J. A. E., and Meet, W. J.: Studies on Venous Pressure, ibid. **95**:294, 1930.

8. Schneider, E. C., and Truesdell, D.: The Effects on the Circulation and Respiration of an Increase in the Carbon Dioxide in the Blood of Man, Am. J. Physiol. **63**:155, 1922. Gollwitzer-Meier, K.: Venöse Rückflussregulierung und Venomotorenfunktion unter dem Einfluss der Kohlensäure, Ztschr. f. d. ges. exper. Med. **69**:377, 1930. Méan.[3t]

9. Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Effects of Electrically Induced Convulsions upon Respiration in Man, Am. J. Psychiat. **103**: 680, 1947.

stricts veins and elevates venous pressure is well known.[10] It has been stated that persistent marked slowing of the heart induced by vagal stimulation may likewise give rise to increases in venous pressure;[11] Méan,[3t] however, could not demonstrate this effect in man. At any rate, it is probably not a factor in the present study, as vagal slowing of the heart is transitory and at most only moderate in electrically induced seizure.[12] The tendency of the venous pressure to fall toward the end of the seizure in many instances is difficult to explain; it is to be noted that a fall in arterial pressure also occurs at this time.[1] In observations on venous pressure during electrically induced convulsions, Silfverskiöld and Åmark recorded changes which were often twice as great as those found in the present study. This difference is difficult to interpret but may be due to differences in the violence of the seizures induced.

The return of venous pressure toward normal is likewise the result of the action of many factors. One of these is the aspirating action of hyperventilation, which draws blood from the periphery into the thorax.[13] The importance of this phenomenon is difficult to evaluate in most instances, for the cessation of muscular contractions is usually followed quickly by restoration of respiration. In 4 instances in which apnea persisted, however, it is of interest that the venous pressure remained elevated also and finally decreased with the return of respiratory activity. The sequence of events in these cases suggests that the

10. Capps, J. A., and Matthews, S. A.: Venous Blood Pressure as Influenced by the Drugs Employed in Cardiovascular Therapy, J. A. M. A. **61**:388 (Aug. 9) 1913. Connet, H.: The Effect of Adrenalin on Venous Blood Pressure, Am. J. Physiol. **54**:96, 1920. Brandt, F., and Katz, S.: Ueber die paradoxen Atemschwankungen des Venendrucks beim Menschen, Ztschr. f. d. ges. exper. Med. **76**: 158, 1931. Budelmann, G.: Untersuchungen über den Venendruck die Vitalkapazität der Lunge und das Herzminutenvolumen bei Gesunden und Herzkranken in Ruhe und bei Kreislaufbelastung, Ztschr. f. klin. Med. **127**:15, 1935. Wilkins, R. W.; Weiss, S., and Haynes, F. W.: The Effect of Epinephrine in Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Investigation **17**:41, 1938. Iglauer, A., and Altschule, M. D.: The Effect of Paredrine on the Venous System, ibid. **19**:503, 1940. Plumier.[7b] Eyster and Meet.[7e]

11. Burton-Opitz.[3b] Plumier.[7b] Bayliss, W. M., and Starling, E. H.: Observations on Venous Pressures and Their Relationship to Capillary Pressures, J. Physiol. **16**:159, 1894. Villaret, M.; St. Girons, F., and Grellety-Bosviel, P.: Réflex oculo-cardiaque et tension Veineuse, Compt. rend. Soc. de biol. **86**:1006, 1922.

12. Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Significance of Changes in the Electrocardiogram After Electrically Induced Convulsions in Man, to be published.

13. (*a*) Kroetz.[3h] (*b*) Bedford and Wright.[3j] (*c*) Henderson, Y.; Pruice, J., and Haggard, H. W.: Influence of Forced Breathing on the Circulation, J. Pharmacol. & Exper. Therap. **2**:103, 1918.

aspirating effect of breathing is the important factor, although it must be borne in mind that the onset of hyperventilation may also cause a decrease in venous pressure by lowering the carbon dioxide content and tension of the blood.[13c] Failure of the venous pressure to return to the control level after a convulsion in spite of hyperventilation might be explained on the basis of some remaining increase in blood carbon dioxide tension [9] and possibly also persistence of abnormally great sympathetic activity. The fact that Silfverskiöld and Åmark [1] failed to note the common occurrence of final levels of venous pressure above the control values may be a consequence of the fact that their initial values were too high; i. e., their patients were inadequately relaxed.

Too little is known of the changes in circulatory dynamics during electrically induced convulsions to define the effects of the variations in venous pressure observed. It is known, however, that the pronounced rises in venous pressure observed in electric shock or metrazol convulsions are associated with an increase in cerebrospinal fluid pressure [14]; like the venous pressure, the cerebrospinal fluid pressure may remain somewhat elevated after the end of the convulsion.[14b] It is of interest that rises in the spinal fluid pressure occasionally to levels as high as 1,000 mm. have also been reported in the Valsalva experiment.[15] The cardiac output also shows a transitory decrease at the height of the Valsalva procedure.[3v] The lowered cardiac output and the increases in venous and cerebrospinal fluid pressures probably result in transitory slowing of the circulation in the brain, or at least partial neutralization of the effects of hypertension and hypercardia in increasing cerebral flow.

The magnitude of the increase in venous pressure observed raises the question as to the possible production of capillary hemorrhages in the brain and elsewhere. This consideration is of considerable importance, for increased capillary fragility is well known to occur in malnutrition and has also been described in elderly or in hypertensive persons.[16] It is to be noted, however, that even in the presence of greatly increased capillary fragility it is necessary to increase the venous pressure to a considerable degree for from five to fifteen minutes in order to produce cutaneous petechiae, whereas the marked venous

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14. (*a*) Silfverskiöld and Åmark.[1] (*b*) Niketic, B., and Susic, Z.: Bemerkungen über das Verhalten des Liquor cerebrospinalis während des Cardiazolkrampfes, Arch. f. Psychiat. **108**:562, 1938.

15. Bürger.[3g] Nordenfeldt.[3q] Hamilton and others.[3y]

16. Schrader, R.: Ueber Veränderungen im Vorhalten der Dichte der Kapillarwandung und deren Nachweis durch das Endothelsymptom, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **34**:260, 1921. Beaser, S. B.; Rudy, A., and Seligman, A. M.: Capillary Fragility in Relation to Diabetes Mellitus, Hypertension and Age, Arch. Int. Med. **73**:18 (Jan.) 1944.

hypertension which occurs during electrically induced convulsions is of less than a minute's duration. It is unlikely, therefore, that the changes observed in venous pressure during a short convulsive seizure create much danger of extensive intracerebral hemorrhage. The observation of Silfverskiöld and Åmark [1] that the rises in venous pressure in the jugular vein may at times be of minor degree are not entirely acceptable in view of the difficulties these authors experienced in measuring pressure in that vein.

That the Valsalva maneuver is at times hazardous is well known. Liedholm [37] reviewed the material bearing on the untoward effects of that procedure on patients with cardiac disease, and more recently Chapman and Linton [38] analyzed its dangers in patients with phlebitis. Modification of the convulsive seizure by means of curare, for instance, greatly reduces the rise in venous pressure which occurs [17]; convulsions so modified are apparently equal in therapeutic effect to more violent seizures, and it is therefore clear that the circulatory changes which accompany pronounced rises in venous pressure are not essential to clinical improvement.

SUMMARY AND CONCLUSIONS

Electrically induced convulsions cause marked transitory elevations in venous pressure consequent to muscular straining, the Valsalva phenomenon, increased carbon dioxide tension of the blood and possibly also increased circulating epinephrine. After termination of the seizure the venous pressure remains slightly elevated. It is concluded that the pronounced increases in venous pressure are of such short duration as to create little hazard of inducing intracerebral capillary hemorrhages. That other hazards exist is, however, recognized. It is concluded that the marked rise in venous pressure and the circulatory changes associated with it are not essential to obtaining clinical improvement.

McLean Hospital.

17. Altschule, M. D., and Tillotson, K. J.: Modification by Means of Curare of the Circulatory Changes Occurring During Electrically Induced Convulsions in Man, to be published.

RECURRENT ARACHNOIDITIS IN THE DORSAL SPINAL REGION

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ALTHOUGH information is rapidly accumulating concerning spinal arachnoiditis, confusion still exists regarding many aspects of the diagnosis and prognosis of the disease. Much of this confusion arises from a failure to realize that arachnoiditis may be associated with considerable variation in its etiology, location, pathologic process, individual response and clinical course.[1] The present cases are reported to illustrate in particular the exacerbation-remission type of course frequently seen in patients with spinal arachnoiditis. Such fluctuations in clinical manifestations explain many controversial elements concerning physical changes, abnormalities of the spinal fluid and prognosis.

CLINICAL MATERIAL

The 4 cases presented were selected from 8 cases of dorsal arachnoiditis of the dorsal spinal region studied at the Strong Memorial Hospital. The diagnosis was verified in 2 cases at operation and indicated in the remaining 2 cases by virtue of compatible clinical manifestations and subarachnoid studies.

REPORT OF CASES

CASE 1.—A woman aged 51 had an attack of polyarthritis and "sciatica" on the left side coincident with a severe erysipeloid infection of the left ear twelve years before her first admission to the hospital. Three years before admission a similar attack occurred, supposedly with a bout of tuberculous cervical adenitis. Twelve days before admission—two months following a recurrent infection of the left middle ear—pain and numbness developed in the right hand and arm, followed by numbness of the right side of the trunk and the right leg. Pain and paralysis in the right leg, weakness in the left leg and retention of urine rapidly followed.

At the time of admission she was found to have bilateral chronic infection of the middle ear and deafness. Neurologic examination revealed a questionable weakness of the left side of the face and pronounced but patchy bilateral sensory changes below the eighth cervical dermatome. There was weakness of the right upper extremity and of both lower extremities, amounting to almost complete paralysis of

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1. Ramsey, G. H. S.; French, J. D., and Strain, W. H., in Pillmore, G. U.: Clinical Radiology: A Correlation of Clinical and Roentgenological Findings, Philadelphia, F. A. Davis Company, 1946, pp. 132-134.

the right leg. Deep reflexes were greatly increased throughout, and Babinski's sign was present bilaterally. Lumbar puncture revealed normal manometric readings. The spinal fluid contained 50 mg. of protein per hundred cubic centimeters and 59 leukocytes per cubic millimeter.

A chronically infected left antrum was corrected surgically, and infected teeth were removed.

Eight months later a letter from the patient's physician reported that her sensation, reflexes and muscular power were normal and that she had resumed normal activities.

Approximately one year later, coincident with a streptococcic infection of the throat, she had a similar bout of paraplegic motor and sensory changes. She was said to have been given an autogenous vaccine and to have again almost completely recovered after several months.

About nine months before readmission to the hospital she began to have gradually increasing numbness, spasticity and weakness of both legs and the left arm. There was also increasing bladder difficulty.

On readmission to the hospital, she was found to have marked spasticity with increased deep reflexes and to present Babinski's sign in both lower extremities. Hypesthesia in a glove and stocking distribution was present in the left hand and in both feet. Lumbar puncture revealed normal dynamics, and the protein content of the fluid was 35 mg. per hundred cubic centimeters. A myelogram showed no abnormality. She was discharged unimproved.

Comment.—This patient had five exacerbations of a similar neurologic disease in a period of nineteen years. During two of these illnesses she was studied at the Strong Memorial Hospital. The early episodes were mild and infrequent, but the later attacks were severe and associated with persistent disability. Of particular interest is the fact that during one illness the spinal fluid protein was increased twelve days after onset, whereas seven years later it was normal nine months after another exacerbation. The etiologic factor in this case seems to be significantly associated with infections of the sinuses, ears and teeth.

CASE 2.—A man aged 30 gave a history of bouts of pain in the chest associated with a productive cough. These episodes lasted one week and had occurred over a period of five years prior to his first admission to the hospital, in 1936. One year before his admission a similar episode, lasting ten days, was assocated with sphincteric disturbances and weakness in the legs. These symptoms gradually subsided over a period of two months. Two weeks before his admission to another hospital cough and pain in the chest again developed, followed rapidly by weakness and tingling in the legs. He was found to have an inconstant sensory level at the fifth dorsal dermatome, spastic gait, increased deep reflexes of the lower extremity with ankle clonus and absence of the abdominal reflexes. Studies of the subarachnoid fluid were reported to show a partial block and "enormous increase" in spinal fluid protein.

On admission to the Strong Memorial Hospital two weeks later he was found to have patchy sensory changes up to the fifth dorsal dermatome. Spastic weakness with increased deep reflexes were present in the legs, and the abdominal reflexes were absent. The Babinski sign was not present. Lumbar puncture at this time showed a questionable block with a spinal fluid protein reading of 7 mg. per hundred cubic centimeters, and myelographic studies demonstrated a partial

block at the level of the first dorsal vertebra. Surgical exploration at this level revealed cystic arachnoiditis, and the cyst was opened.

After operation the patient was greatly improved, but he returned two months later with a similar, if milder, episode. Lumbar puncture again showed a partial block and the protein content of the fluid was reported to be "moderately increased."

Nine years later he reported by mail that similar episodes of diminishing frequency and intensity occurred at yearly intervals but that he had been completely well for two years.

Comment.—This patient had many attacks of arachnoiditis over a period of fourteen years, supposedly associated with repeated pulmonary infections. In two acute episodes the spinal fluid protein was found to be increased. In one instance the reading was very low two weeks after the protein content had been reported to be "enormously increased." The diminishing severity of attacks, culminating in complete subsidence of symptoms, in this case is contrary to the more frequent progression of symptoms.

CASE 3.—An Italian laborer aged 52 first noted vague pain in the right upper abdominal quadrant two months before admission to the hospital. This became more severe two weeks before admission, was worse on coughing and straining and was of "girdle" type. He also reported some pain and subjective numbness in his fingers and legs. There were a loss of 25 pounds (11.3 Kg.) in weight and a feeling of generalized weakness. The past history revealed that he was known to have had diabetes for three years but was not taking insulin.

On examination the patient appeared chronically ill. Patchy hypesthesia corresponding to the tenth dorsal dermatome was present. Reflexes were absent in the lower extremities, and Babinski's sign was not present. There was weakness of the right abdominal wall on straining as well as weakness of both legs.

A lumbar puncture revealed normal manometric readings, but the fluid had a protein content of 400 mg. per hundred cubic centimeters. Three days later the protein determination showed a level of 100 mg. per hundred cubic centimeters, and a week later it was 15 mg. per hundred cubic centimeters.

The patient was discharged as improved but returned to the hospital two weeks later because of recurrence of symptoms. The physical findings on this occasion were similar to those previously reported but were somewhat more pronounced. He now showed a sensory level as high as the fourth dorsal dermatome, and cutis anserina was occasionally noted in the hypesthetic areas. A lumbar puncture four weeks after the first subarachnoid studies revealed evidence of partial block, and the fluid showed a total protein content of 600 mg. per hundred cubic centimeters. A cisternal myelogram with "pantopaque" (a mixture of ethyl esters of isomeric iodophenylundecylic acids) showed irregularity and fragmentation of the visualized column in the midthoracic region (figure), and the protein content of the cisternal fluid was 15 mg. per hundred cubic centimeters. Exploratory laminectomy was performed at the level of the seventh to the ninth dorsal spine, and a milky, thick arachnoid adherent in many places to an atrophic-appearing cord was encountered. The adhesions were divided so far as was possible.

After operation the patient was given radiation therapy, and when seen six weeks after operation he was much improved and ambulatory but still complained of pain in his legs. He died two years later, apparently of disease of the spinal cord.

Comment.—The most remarkable aspect of this case was the rapid and extensive change demonstrated in the subarachnoid studies. The elevated protein level of the spinal fluid fell and partial subarachnoid block disappeared in a week, only to show reversion to a pathologic state two weeks later. Initial improvement was present after operation,

Myelogram taken with "pantopaque" in case 3, showing irregular appearance of the visualized column in the dorsal region.

but a letter from the patient's wife indicated that he died two years later, apparently from a more severe exacerbation of arachnoiditis.

CASE 4.—A farmer aged 30 was hospitalized eleven years prior to his present admission for drainage of multiple epidural abscesses in the dorsal region. He was paraplegic at the time but recovered to the degree that he could work on

his farm without supporting aid. Two weeks before his admission abdominal pain developed, followed by numbness and spasticity in his legs.

On examination, he was found to have such severe spasticity of both lower extremities that he was just able to get about with crutches. There was bilateral hypesthesia of the calves and feet in stocking distribution. The reflexes were hyperactive in the lower extremities, and the Babinski sign was present bilaterally. Bladder function was impaired. A myelogram obtained with "pantopaque" demonstrated a complete block at the level of the first lumbar vertebra. The spinal fluid protein was 375 mg. per hundred cubic centimeters.

The patient began to improve spontaneously and in ten days was able to get around with considerable freedom. The sensory changes had disappeared, and bladder function was normal. Lumbar puncture at this time revealed normal manometric readings and a spinal fluid protein of 30 mg. per hundred cubic centi-

Data on Subarachnoid Studies

Case No.	Time After Onset of Attack	Protein Content of Fluid, Mg./100 Cc.	Manometric Observations	Myelographic Observations
1	2 weeks	50	No block	
	9 months (subsequent attack)	35	No block	No abnormality
2	2 weeks	"Enormously increased"	Partial block	
	4 weeks	7	Questionable block	Partial block first dorsal level
	1 week (subsequent attack)	"Moderately increased"	Partial block	
3	2 months	400	No block	
	10 days later	15	No block	
	3 weeks later	600	Partial block	Irregularity in dorsal region
4	2 weeks	375	Complete block	Complete block at first lumbar level
	4 weeks	30	No block	

meters. Three months later his condition had improved still more but he had not regained full use of his legs.

Comment.—This patient had an acute exacerbation and remission of spinal arachnoiditis eleven years after operation for epidural abscesses in the dorsal region. The rapid transformation of subarachnoid block and high spinal fluid protein to a normal state seen in case 3 was present here. The associated clinical improvement was initially striking, although it was not yet complete three months later.

GENERAL COMMENT

The clinical course of spinal arachnoiditis in most instances is characterized by exacerbation and remission of symptoms.[2] Later, exacerba-

2. Howell, C. M. H.: Arachnoiditis: President's Address, Proc. Roy. Soc. Med. **30**:33-42 (Nov.) 1936. Vincent, C.; Puech, P., and David, M.: Sur le diagnostic, le traitement chirurgical, le prognostic des arachnoïdites spinales, Rev. neurol. **1**:577-595 (April) 1930.

tions may produce neurologic residua suggesting a chronic progressive disease. It is possible at this stage that limiting adhesions or vascular involvement may cause increasing deterioration of the spinal cord,[3] but clinical evidence supports the intermittent nature of the actual inflammatory process. Normal manometric readings and normal protein contents of the spinal fluid may be encountered, therefore, in patients with advanced neurologic changes due to arachnoiditis. Conversely, high protein readings and various degrees of subarachnoid block may be present a few days after the onset of the disease in previously perfectly well persons.

The cases of dorsal spinal arachnoiditis reported here clearly demonstrate the rapid changes which may take place in the subarachnoid system coincident with fluctuation in symptoms. In case 1 no block or alteration in protein was encountered in spite of evidence of advanced involvement of the spinal cord. The patient had experienced a rather severe exacerbation nine months previously, and irreversible changes had obviously occurred in the spinal cord. The other 3 patients, however, were examined during the acute phase of the disease and showed pronounced abnormality in subarachnoid pressure and in the spinal fluid. There is indication, therefore, that spinal arachnoiditis is an acute recurrent process. It becomes chronic only when organized adhesions or cysts have formed, producing irreversible changes in the spinal cord. Changes in subarachnoid pressure and in the spinal fluid appear to follow promptly these fluctuations in symptoms.

Spinal arachnoiditis in the region of the cauda equina has been shown to follow a course of exacerbations and remissions similar to that illustrated here in dorsal arachnoiditis.[4] Involvement of the cauda equina is, in fact, much more common than dorsal or cervical inflammations of this type.

It is of note that "cystic arachnoiditis" was observed at operation in 1 of the verified cases in this group and "adhesive arachnoiditis" in the other. The clinical manifestations, however, were strikingly similar. It is likely that the different types of arachnoiditis described are really only variations of the same process.

In considering the various clinical alterations produced by spinal arachnoiditis, particular attention must be directed to the stage of the disease with which the examiner is involved. Failure to recognize this important point is undoubtedly responsible for the disagreement apparent in available discussions of the subject. The same considerations must be recognized in evaluating the efficiency of various types of therapy and in assigning a prognosis in individual cases.

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3. Stookey, B.: Adhesive Spinal Arachnoiditis Simulating Spinal Cord Tumor, Arch. Neurol. & Psychiat. **17**:151-178 (Feb.) 1927.

4. French, J. D.: Clinical Manifestations of Lumbar Spinal Arachnoiditis, Surgery **20**:718-729 (Nov.) 1946.

The similarity of spinal arachnoiditis and other diseases characterized by albuminocytologic dissociation frequently makes differentiation impossible.[5] Further clinical and pathologic observations are necessary to record the actual interrelationship of diseases of this group.

SUMMARY

Four cases of dorsal spinal arachnoiditis are presented in which exacerbation and remission over long periods characterized the course of the disease.

Rapid and repeated changes in subarachnoid block and protein content of the spinal fluid occurred coincident with the recurrence of clinical symptoms.

Such fluctuation in clinical manifestations is the basis for disagreement concerning many aspects of spinal arachnoiditis.

University of Rochester School of Medicine and Surgery.

5. Casamajor, L., in discussion on Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: A Clinical and Pathological Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis, Arch. Neurol. & Psychiat. **35**:937-963 (May) 1936.

SCHISTOSOMIASIS JAPONICA WITH INTRACEREBRAL GRANULOMA; OPERATIVE REMOVAL WITH RECOVERY

Report of a Case

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SCHISTOSOMIASIS japonica, or Oriental schistosomiasis, being limited to foci in Japan, Formosa, China, the Philippines and the Celebes, is rarely seen in this country. Cerebral symptoms and manifestations of this infection are experienced even more uncommonly.

The first of such cases was published in 1906 by Tsunoda and Shimamura.[1] Their patient experienced indigestion and abdominal pain in 1901, began to have convulsive seizures with loss of consciousness and aphasia in 1903 and, after a series of right-sided convulsions, presented a right hemiplegia. Autopsy, in August 1904, revealed diffuse thickening of the cerebral meninges, with abnormal masses in the left parietal region, partly in the gray and partly in the white matter, as well as a zone of softening involving the internal capsule, the optic thalamus and the basal ganglia on the left side. The ova were also discovered in the choroid plexus and the spinal cord.

In 1935 Nieva [2] described the symptoms of a patient from Borongan, Samar, who complained of generalized numbness, dizziness, headache and convulsive episodes, accompanied with loss of consciousness. The feces

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Read at the combined meeting of the medical and surgical staffs of Hammond General Hospital Oct. 12, 1945; at the staff meeting of the Santa Barbara Cottage Hospital June 24, 1946, and at the meeting of the American Academy of Neurological Surgery, Hot Springs, Va., Sept. 11, 1946.

1. Tsunoda, T., and Shimamura, S.: Beiträge zur pathologischen Anatomie der sogenannten Katayama-Krankheit, zur Aetiologie der Hirngefässembolie und der Jackson'schen Epilepsie, Wien. med. Wchnschr. **56**:1681, 1906.

2. Nieva, D. E.: Epileptiform Convulsions Probably Due to Schistosomiasis, Bull. San Juan de Dios Hosp., 1935, no. 7, p. 9.

of the patient contained the ova of Schistosoma japonicum, and the diagnosis of probable cerebral schistosomiasis was made by inference from the fact that the patient improved with injections of antimony potassium tartrate and emetine hydrochloride.

In 1936 Africa, de Léon and Garcia [3] reported a case in which the ova were associated with a fatal hemorhage into the right basal ganglia of the brain. During the same year Egan [4] described cerebral symptoms and neurologic abnormalities in 2 of his 12 cases in which improvement followed antimony therapy.

Strangely, some of the recent publications have overlooked the 2 cases in which Mr. Julian Taylor and Sir Percy Sargent performed operation and which were reported by Greenfield and Pritchard [5] in 1937. In each case an unsuspected granuloma containing the eggs of S. japonicum was removed surgically from the left parietal region of the brain, with clinical recovery. The first patient, a lieutenant in the Royal Navy, had a series of epileptic attacks at the age of 30, about four years after having been exposed in China to water endemic for schistosomiasis. Except for an attack of diarrhea, lasting about three weeks, without any recorded febrile disturbance or any irritative cutaneous rash, and the history of exposure, there was nothing to suggest the disease. At the time of his seizures, the patient believed that he was in excellent health. He described a visual aura of flashes of light in the obscured vision of the right peripheral field, and subsequently aphasic symptoms associated with clumsiness in the use of the right hand became evident.

Ventriculographic studies, performed by Mr. Taylor, disclosed narrowing of the left lateral ventricle, with forward displacement of the body and posterior horn, and failure of filling of the left temporal horn. The third ventricle was narrowed and displaced slightly to the right. These observations corroborated the clinical impression of a tumor in the left parieto-occipital region.

Mr. Julian Taylor operated on Jan. 20, 1936, removing a friable, yellow mass from beneath the surface of the brain in the suspected area, and pathologic examination revealed this to be a granuloma containing the eggs of S. japonicum. The patient was given a total dose of 30 grains (1.95 Gm.) of antimony tartrate intravenously and made an uneventful recovery. His residual symptoms included grossly defective visual stereognosis in the right visual field and occasional attacks of dizziness

3. Africa, C. M.; de Léon, W., and Garcia, E. Y.: Heterophydiasis: III. Ova Associated with a Fatal Hemorrhage in the Right Basal Ganglia of the Brain, J. Philippine Islands M. A. **16**:22, 1936.

4. Egan, C. H.: An Outbreak of Schistosomiasis Japonica, J. Roy. Nav. M. Serv. **22**:6, 1936.

5. Greenfield, J. G., and Pritchard, B.: Cerebral Infection with Schistosoma Japonicum, Brain **60**:361, 1937.

with associated aphasia. Up to June 1937 he had experienced only one episode of unconsciousness, lasting about thirty minutes.

Their second patient, also a lieutenant in the Royal Navy, experienced severe generalized headaches, more pronounced in the left parietal region and associated with occasional morning vomiting. Impaired vision was noted in the right temporal field, and on examination papilledema and right lower quadrantic hemianopsia were discovered. Operation was performed on Sept. 15, 1930 by Sir Percy Sargent, who removed subtotally a large tumor from the upper part of the left parieto-occipital region. This mass revealed a pathologic picture quite similar to that in the first case. Subsequently, the patient was treated with antimony potassium tartrate. At his last reported examination, in June 1931, he stated that he was fairly well. Examination disclosed only right homonymous hemianopsia and slight astereognosis of the right hand.

Interestingly, in neither case was there any symptom to suggest the nature of the infection, and in each operation was performed for supposed glioma.

In 1941 Vitug, Cruz and Bautista [6] reported 2 cases of schistosomiasis in which cerebral symptoms were produced almost exclusively, with improvement following the use of stibophen ("fuadin" ; sodium antimony III bis-catechol-2, 4-disulfonate) in 1 case and with confirmatory necropsy observations in the other.

Billings, Winkenwerder and Hunninen,[7] in 1946, reported their clinical study of 337 cases of acute schistosomiasis japonica in the Philippine Islands, with the results of stibophen therapy in 110 cases. In 7 cases neurologic symptoms developed, but in only 3 were the manifestations of a severe character, including hemiplegia and other cerebral symptoms. Improvement followed stibophen therapy. In their opinion, the onset of the cerebral symptoms and peripheral neurologic signs, indicating extensive involvement, was so abrupt that it was difficult to believe that the changes were due solely to deposition of ova. Inasmuch as there were simultaneously rather extensive urticaria and angioneurotic edema, the possibility that cerebral edema played a role was considered likely. During the same year, Carroll [8] described 5 cases of cerebral involvement complicating schistosomiasis japonica; neurologic involvement was apparent in the acute stage of the disease in 4 of these cases and four months after the acute stage in 1 case.

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6. Vitug, W.; Cruz, J. R., and Bautista, L. D.: Schistosomiasis Involving the Brain: Two Case Reports, J. Philippine Islands M. A. **21**:291, 1941.

7. Billings, F. T.; Winkenwerder, W. L., and Hunninen, A. V.: Studies on Acute Schistosomiasis Japonica in the Philippine Islands: I. A Clinical Study of Three Hundred and Thirty-Seven Cases with a Preliminary Report on the Results of Treatment with Fuadin in One Hundred and Ten Cases, Bull. Johns Hopkins Hosp. **78**:21, 1946.

8. Carroll, D. G.: Cerebral Involvent in Schistosomiasis Japonica, Bull. Johns Hopkins Hosp. **78**:219, 1946.

As can be appreciated from a review of the literature, only 2 other cases have been reported in which the intracranial granuloma was removed surgically with clinical recovery. For this reason, and because similar experiences may be anticipated subsequently as the result of large numbers of troops having been stationed in infected areas, it is believed important to describe the first experience of this kind in this country.

REPORT OF CASE

History.—In January 1945 a soldier, aged 29, on duty in the Southwest Pacific area, and previously in excellent health, experienced the onset of diplopia, followed by frequently recurring headaches. The diplopia persisted for four months before subsiding, but the headaches continued and increased in severity gradually. Convulsive episodes occurred. The first seizure, in January, led to his hospitalization until March. He was again hospitalized for a week after his second attack, in May, and after his return to the United States he experienced his third convulsion, on Aug. 18, 1945.

The convulsions were preceded by the prodromal symptom of a flash of light, which was not lateralized. No history of biting the tongue or of incontinence was obtained. In the last episode the patient recalled a spasmodic jerking of the left side of the face, but no other detail of the pattern of the attack was noted. After the periods of unconsciousness, the patient recalled no weakness of his extremities or any other lateralizing sign.

The information was obtained of a minor head injury sustained during a blackout in December 1944, while the patient was on an LST, during an invasion of Mindoro Island. There was no unconsciousness or apparent sequela. The past history disclosed nothing else of a contributory character.

Examination.—Because of the probability of an intracranial expanding lesion, the patient was transferred from the Oakland Area Regional Hospital to Hammond General Hospital in Aug. 29, 1945. General physical examination revealed nothing unusual. The patient was mentally alert, cooperative and in no acute distress, although he complained of a constant generalized headache. The temperature, pulse and blood pressure recordings were normal. A complete blood count and urinalysis revealed nothing unusual, and the Kahn reaction of the blood was negative.

Neurologic examination uncovered the following abnormalities: bilateral papilledema; slightly impaired stereognosis on the left side as compared with that on the right, associated with slight weakness of the left hand grip, and a higher-pitched percussion note on the right side of the calvaria than on the left. Ophthalmologic consultation confirmed the presence of bilateral papilledema of approximately 1 D., and normal peripheral fields with enlargement of the blindspots consistent with the papilledema were reported.

Roentgenograms of the chest demonstrated no evidence of pulmonary or cardiac disease, but those of the skull revealed that the calcified pineal body, seen in its normal position in the lateral views, was displaced 1.1 cm. to the left of the midline in the anteroposterior projection. The electroencephalographic recordings, on Sept. 4, 1945, showed predominantly low voltage and fast activity in all leads, with occasional 9 per second activity. No focal signs or responses to hyperventilation were observed. Occipital asymmetry with increased amplitude in the left occipital region was evident.

On September 4 a spinal fluid pressure of 200 mm. was obtained and 15 cc. of clear, colorless fluid removed, which contained 70 mg. of protein per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was 2 plus and the colloidal gold curve 544321110. The second lumbar puncture, on September 10, showed a pressure of 430 mm. of spinal fluid. The small amount of clear, colorless fluid removed contained 1 cell per cubic millimeter; the Wassermann and Kahn reactions were negative; the colloidal gold curve was normal.

In the absence of any history of syphilis or evidence of a penile lesion, it seemed difficult to explain the clinical findings on the basis of syphilis or gumma of the central nervous system, and it was believed that the one positive Wassermann reaction of the spinal fluid represented a false positive one. The clinical impression was that of an intracranial expanding lesion in the right temporo-occipital area, and because of the history of a previous minor head injury the possibility of a subdural hematoma was entertained.

In spite of the localizing clinical signs, it was believed advisable to precede operative intervention with a ventriculographic study, and this was performed on September 19, with the use of local anesthesia. Approximately 20 cc. of air was injected and a similar amount of ventricular fluid removed from the posterior horn of the left ventricle. The ventriculograms revealed shifting of the well filled ventricular system to the left side, and this included a similar displacement of the third ventricle. There was a noticeable filling defect of the posterior and temporal portions of the right lateral ventricle, which appeared flattened and depressed. It was believed that these changes confirmed the impression of an expanding lesion in the right temporo-occipital region.

Operation and Diagnosis.—With anesthesia induced with solution of tribromoethanol U. S. P. and ether, a small osteoplastic craniotomy flap was turned down in the right occipitoparietal region in the usual manner. The bone in the subtemporal region was rather thin. A small portion of bone in this region was removed for decompression. The dura, which was tense, was opened in the posterior portion of the operative field to uncover tumor tissue overlying the corresponding area of the cortex. Small, whitish tubercles, from a pinpoint to a pinhead in size, were noted on the surface of the tumor; and as the indurated and rubbery tumor was removed piecemeal, it was observed to contain small calcified areas, but no caseation was apparent. The tumor tissue seemed to extend in a cluster, or racemose-like arrangement of granulomatous material, the portions varying in size. With removal of all this tissue, which extended into the subtemporal region and comprised a mass the size of an orange, the intracranial pressure was relieved. The nature of the granuloma was not determined at this time, and it was the operator's impression that the tumor was an unusual type of glioma which allowed nothing further to be accomplished surgically.

At first the diagnosis of the removed tumor was puzzling. Its similarity to both a tuberculoma and a gumma was misleading, and only after additional study and examination was the unusual and unexpected diagnosis of schistosomiasis japonica arrived at.

Pathologic Report.—The specimen consisted of many moderately firm pieces of grayish, mottled tissue, the largest measuring 3.0 cm. in maximum diameter. The pieces of tissue were tough and rubbery, showed no definite architecture but had numerous grayish areas of necrosis. On section, one portion of the specimen presented a homogeneous, grayish, glistening surface, was quite firm and in various planes had lighter grayish lines running through it. Sections of most of the pieces, however, disclosed a yellowish area of caseous-appearing necrosis scattered irregularly throughout.

A frozen section revealed areas of caseous necrosis and inflammatory cells. All the cysts were apparently lost in cutting, for none was observed in the frozen section material, either with the rapid methylene blue stain or with the hematoxylin and eosin stain.

The paraffin section presented a striking picture, with some of the oval cystic structures appearing in nearly every field. Careful search was necessary, however, to find any with spines sufficiently characteristic to be of value in determining the

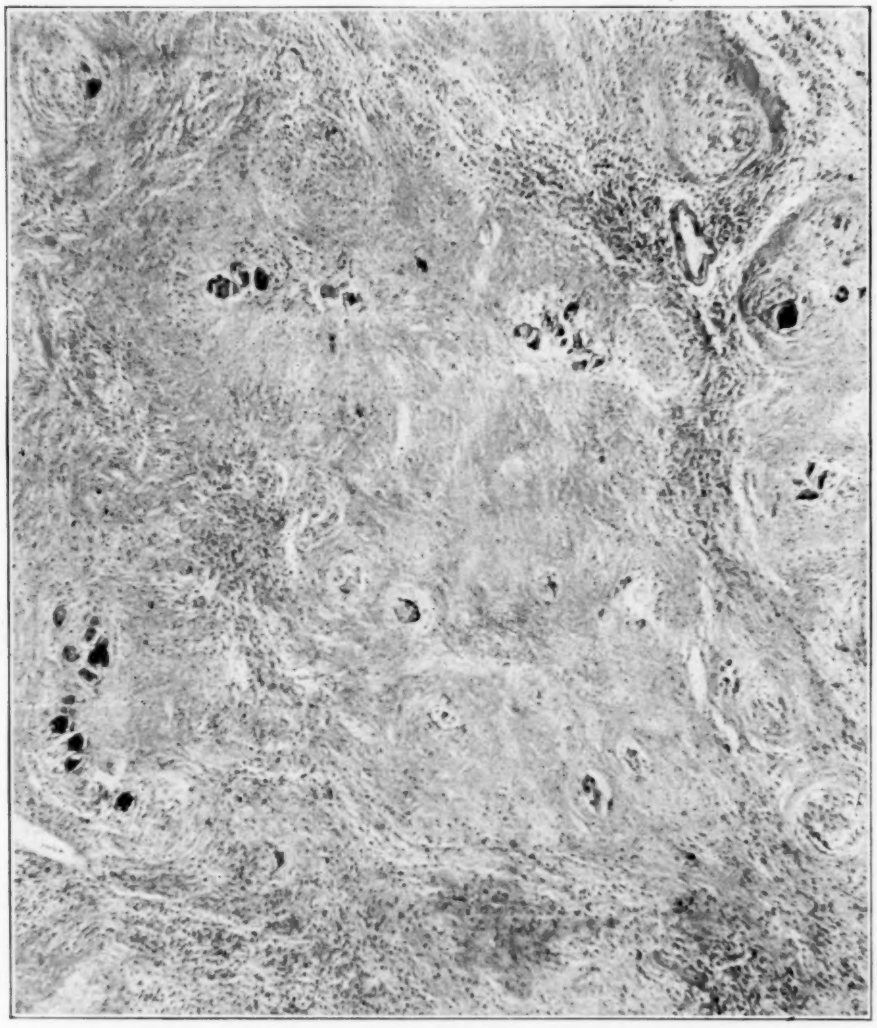

Fig. 1.—Photomicrograph (× 100) showing numerous ova in the granulation tissue (United States Army Medical Museum Neg. No. 90755).

type of organism. The general appearance of the tissue was that of an extensive granuloma with large areas of caseous necrosis, around which were clusters of the cysts of the parasite. In some places these cysts appeared in large groups, while in others they occurred singly or in groups of two or three. The tissue reaction about the caseous areas was one of gliosis, with the scattered appearance of giant cells of

the Langhans type. Varying amounts of cellular infiltration, comprised of eosinophils, and less frequently of mononuclear phagocytes and plasma cells, were observed.

The ova were characterized by their doubly refractile walls and darkly stained granules, which appeared about the size of the lobe of the nucleus of a polymorphonuclear leukocyte, and by their oval shape. On some of these ova spinous

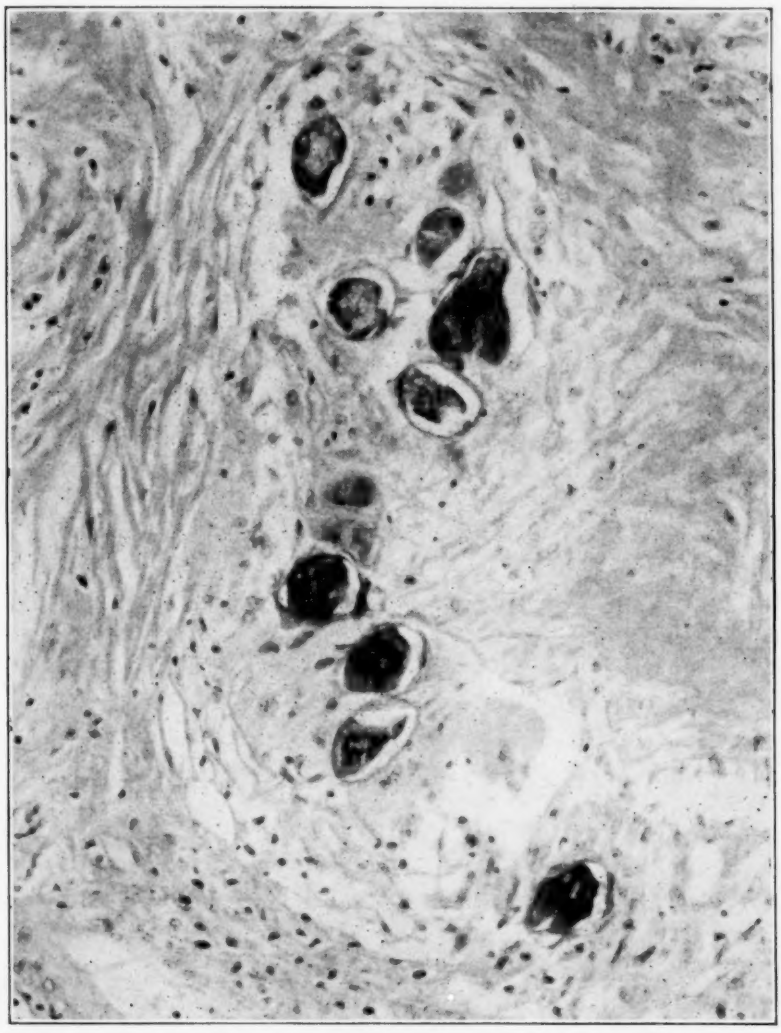

Fig. 2.—Photomicrograph (× 250) showing some of the ova in granulation tissue of the removed tumor (United States Army Medical Museum Neg. No. 90756).

projections were observed on the side near one end, and rarely what appeared to be a terminal spine was seen.

A striking picture of apparent formation of miliary granulomatous areas surrounding the larger caseous areas was also noted. These granulomatous areas occurred singly and in groups as miliary and conglomerate tubercles, which usually

were composed of single or multiple parasitic cysts, epithelioid cells and glial cell proliferation. Frequently these epithelioid cells contained one or more giant cells with peripheral nuclei, and usually they were surrounded by dense glial tissue, having the appearance of a hyaline collar.

Over the surface of the tumor there was thickening of the leptomeninges, which was associated with increased vascularity and leukocytic infiltration, predominantly lymphocytic in character, with a few plasma cells and eosinophils.

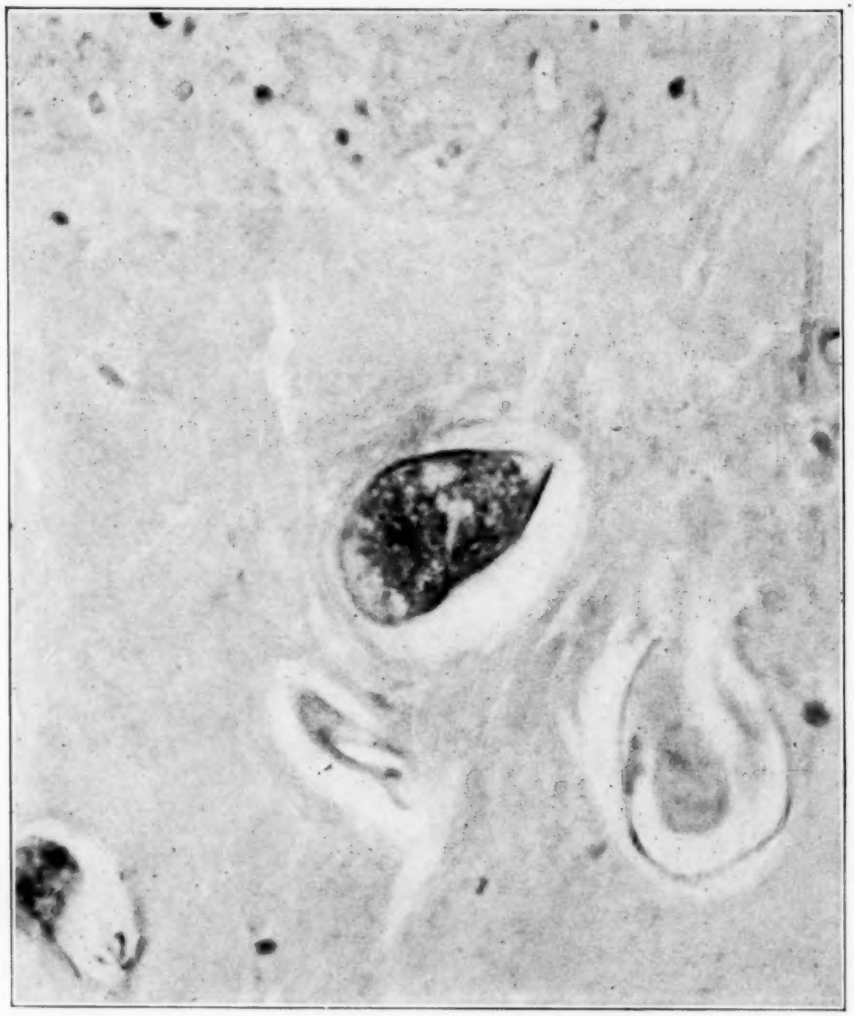

Fig. 3.—Photomicrograph (× 480) showing a higher power view of the ova (United States Army Medical Museum Neg. No. 90757).

The pathologic diagnosis was granuloma of the brain (schistosomiasis).

Postoperative Course.—In view of the unusual observation, the patient was interviewed again concerning a history relative to schistosomiasis. He told of being overseas at Finchaven and New Guinea for about five months, and at Hollandia, Netherlands New Guinea, for approximately four months. He was on Leyte on

Oct. 20, 1944 and remained there about one month, after which he went to Mindoro with his outfit. While on Leyte, he occasionally bathed in fresh water streams, in an area endemic for schistosomiasis japonica, and the infection was undoubtedly picked up there. Surprisingly, he gave no history of symptoms usually associated with the condition, and nothing, moreover, was found on general physical examination.

After the diagnosis had been established, the stools were examined repeatedly for ova, but none were found. Repeated urinalysis also disclosed nothing unusual. Repeated blood counts revealed a slight eosinophilia on only a few occasions, and likewise a slight leukocytosis. Anemia was never evident. The patient was placed under treatment with potassium iodide for a month, and he was also given a course of stibophen, totaling 80 cc.

Ophthalmologic examination after operation disclosed that the papilledema had receded and, again, that the peripheral fields were normal, but the enlargement of the blindspots was still evident.

Although for approximately four weeks the patient noticed no improvement in his headaches, the postoperative course was essentially uneventful. With the closure of the Hammond General Hospital, he was transferred to the Ashford General Hospital at White Sulphur Springs, W. Va., for further observation, treatment and disposition. A letter written by him there, on Jan. 25, 1946, stated that about Dec. 10, 1945 his headaches had ceased completely and that "all in all, I feel pretty good except that I get shaky once in a while."

A second letter from the patient written on April 16, 1946, told of his getting treatments with antimony potassium tartrate, the first of which left him weak and tired for a few days. No mention was made of his condition otherwise, and he wrote that he was looking forward to his discharge from the service some time prior to June.

The patient's third letter, written on June 24, 1946, is quoted as follows: "You can say that May 15 was my lucky day. I've been discharged from the Army. I haven't been doing much of anything since I left. The only work I'm doing now is around the house, and it seems that I can't do much of that. My legs seem to give out, and I have to sit down for a while. I often take little walks to get some of my strength back in my legs. I still have occasional headaches on the right side and in the back of my head. I haven't had any sort of spells for quite a while, and I hope I don't. This is about all I can say, Doctor, and I shall write again soon."

HISTORICAL REVIEW [9]

While the present paper is concerned primarily with the uncommon feature of schistosomiasis japonica affecting the central nervous system, and although a detailed consideration of the history, pathogenesis, treatment and course of schistosomiasis is available in the standard textbooks of parasitology, it seems hardly appropriate to omit entirely a discussion of these important phases of the subject.

A Japanese physician, Fujii, first mentioned the disease in 1847. The eggs of the parasite were discovered in various organs of patients in 1890 by Yamagiwa, who ascribed the etiologic role in the infection to the eggs. The eggs were first observed in the feces by Kasai in 1903. The

9. Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 3, Philadelphia, Lea & Febiger, 1943, p. 385.

female worm was discovered in the portal vein by Fujinami in 1904, by Miyagawa in 1912 and by Miyairi and Suzuki in 1913.[9]

ETIOLOGIC AGENT[10]

In contrast to other trematodes, the adult worms of the schistosomes parasitic in man have separate sexes. Some of the eggs deposited in the small venules of the intestinal wall by the female worm are extruded and discharged into the feces, where in a few hours they are hatched, to liberate a ciliated, free-swimming larva, or miracidium. This larva invades the soft tissues of the intermediate host, an appropriate amphibious snail, in which asexual multiplication occurs and results in the production of numerous, free-swimming, fork-tailed cercariae, which are discharged only when the snails are at or below water level. Only certain species of amphibious snails are suitable for the larval development of S. japonicum, and sources of infection are limited to regions where these species are present. The molluscs are small and are most abundant in still water.

Infection generally is acquired by contact with water infected with cercariae. On contact with the skin of mammals which enter infected water, the cercariae cast off their tails and in the course of twenty-four hours penetrate to the cutaneous capillary beds, enter the venous circuation and are carried through the right side of the heart to the lungs; from there they filter through the pulmonary capillaries into the chambers of the left side of the heart to the systemic circulation. Only the parasites reaching the intrahepatic portal circulation via the mesenteric artery and capillaries proceed to feed, grow and migrate to the branches of the mesenteric veins. In the mesenteric venules the mature worms are paired sexually, and here egg deposition occurs. These eggs pass through the submucosa and mucosa and are extruded into the lumen of the bowel, together with extravasated blood.

Greenfield and Pritchard[11] considered two methods by which the ova may reach the brain. In the first, the circulating ova which pass the barrier of the liver and the lungs arrive embolically; in the second, the circulating larvae develop into adults in the veins of the brain instead of in the portal system and the ova are extruded in situ. In their cases, as in our case, the cerebral lesions were mainly in the posterior part of the parietal lobes, suggesting that the eggs were deposited by the female either in or near the place where they were observed. While in their opinion it was possible, it seemed unlikely that a very large number of eggs might be carried by the blood stream to one part of the brain, and

10. Craig and Faust.[9] Schistosomiasis Japonica, Bull. U. S. Army M. Dept. **4**:273, 1945.

11. Greenfield and Pritchard.[5] Chalgren, W. S., and Baker, A. B.: Tropical Diseases: Involvement of the Nervous System, Arch. Path. **41**:66 (Jan.) 1946.

more probable that the adult worms were lying in one of the cerebral venous sinuses. The authors noted that it would be easy for the female to pass a certain distance up the posterior anastomotic vein from the lateral sinus and to lay her eggs in the smaller venous radicles entering this vein.

COURSE AND SYMPTOMATOLOGY [12]

Because of the frequently transient character of the initial symptoms, they often pass unobserved; for this reason, a history of exposure is most important diagnostically, particularly in a group of patients with the same exposure and clinical course.

Immediately after exposure, itching and a papular rash may occur, but usually the first symptoms are manifest three to ten weeks later. These may include chills and fever, itching, unproductive cough, headache, nuchal stiffness and pain, pain in the chest or epigastrium and general abdominal discomfort or cramplike pain. Anorexia and loss of weight often are striking, but diarrhea usually is not severe. Urticaria, edema, signs suggestive of bronchopneumonia and abdominal tenderness may be present, and enlargement of the lymph nodes may be demonstrable. Uncommonly, signs of involvement of the central nervous system appear. The liver and, later, the spleen are often palpable. Roentgenograms of the lungs may reveal scattered areas of infiltration.

In the early stages, the blood picture shows a rapidly increasing white cell count with pronounced eosinophilia, without any significant anemia. After egg deposition has been initiated, the stools may contain mucus and blood as well as eggs, and this diarrhea often persists from two to ten weeks. While there may be relapses and remissions, if reinfection does not occur, spontaneous cessation of early symptoms ultimately takes place in most cases. Eventually, as the result of the reaction of the affected tissues to increasing numbers of eggs deposited in them, an extensive reparative process and proliferation of tissues take place. There may be evident thickening of the intestinal wall; and formation of papillomas, thrombosis of the mesenteric, portal or splenic veins, cirrhosis of the liver, splenomegaly and ascites may be present. Dysentery may recur from time to time, and emaciation and anemia may be severe. At such late stages eosinophilia is rarely present, and the stools seldom contain schistosome eggs.

TREATMENT [10]

Aside from the supportive therapeutic measures usually indicated, the early institution of chemotherapy is the only effective method, and the agents commonly employed are the compounds of antimony, stibophen

12. Faust, E. C., and Meleney, E. H.: Studies on Schistosomiasis Japonica, Monograph 3, Baltimore, American Journal of Hygiene, 1924, p. 339.

and antimony potassium tartrate. Trivalent antimony in the form of stibophen, also known as "fuadin" and neoantimosan, is supplied in ampules containing a 6.4 per cent solution, or about 0.064 grain (4 mg.) of stibophen per cubic centimeter. Ordinarily, the first three doses, of 1.5, 3.5 and 5.0 cc., are given on successive days, while on the subsequent alternate days, providing no toxic effect other than nausea appears, 5 cc. is given until a total of sixteen doses has been administered, or 75 cc. of the solution, containing 0.653 Gm. of antimony.

After an interval of two weeks the course of treatment is often repeated. With stibophen therapy the only commonly occurring toxic symptoms are nausea and vomiting, though rarely joint and muscle pains may be manifest. Depending on the circumstances of the toxic manifestation, the dose is usually reduced or the drug temporarily or permanently discontinued.

Antimony potassium tartrate is preferred by other authors as a more effective therapeutic agent. It is given slowly, by intravenous injection, two or three hours after a light meal, when it is best tolerated; and the patient should remain recumbent for at least an hour after treatment. The first dose is 8 cc. of the 0.5 per cent solution, or 0.04 Gm. of the tartrate, and the subsequent doses, given on alternate days, are increased by 4 cc. on each occasion, or 0.02 Gm. of the tartrate, until a dose of 28 cc., or 0.14 Gm. of tartrate, has been obtained. A total of fifteen injections, or 360 cc. of solution, containing 0.648 Gm. of antimony, is given. Reduction of subsequent doses, or temporary or permanent discontinuance of the drug, depends on the circumstances of the toxic reaction. It is advised that the injection be stopped if a toxic reaction other than coughing takes place.

The toxic effects of antimony potassium tartrate include coughing immediately on injection, which is not considered important; nausea; vomiting; stiffness of the muscles and joints; a sense of constriction of the chest; pain in the upper part of the abdomen; bradycardia; dizziness, and collapse. The course of treatment should not be repeated for at least two weeks.

Since therapy at best leaves much to be desired, the prevention of schistosomiasis is obviously the important consideration and requires avoidance of contact with fresh water infected with cercariae. Moreover, only water treated so that cercariae are killed should be used for bathing, laundry and drinking purposes.

COMMENT

Intracerebral granuloma from infection with S. japonicum is obviously an uncommon experience; according to the literature available, only 2 other patients have been treated neurosurgically, with removal of the granuloma and apparent clinical recovery.

The interesting case we have presented was unusual in that none of the expected symptoms suggesting the etiologic possibility was present, nor was a history of any uncovered from the patient after the diagnosis had been established. Only the history of exposure in the endemic area of Leyte and Mindoro might have given a clue, but in the absence of symptoms and signs otherwise associated with the condition, and in the presence of evidence of an intracranial expanding lesion, it is not strange that the possibility of schistosomiasis was never entertained.

The 2 cases reported by Greenfield and Pritchard [5] were surprisingly similar to our case. The convulsive episodes in their first case occurred four years after exposure to water in an endemic area, and prior to that time the patient had been in excellent health. Except for the history of exposure, there was nothing to suggest the nature of the illness in either patient, and the diagnosis, as in our case, was made only after operation. In their cases the lesion was primarily in the posterior portion of the left parietal lobe; in our case, in the right parietal lobe.

Because of the uncommon observation of the ovar of S. japonicum intracranially, and the similarity of the lesion to the pathologic picture caused by tuberculosis, it is not surprising that tuberculoma was thought to be the likely pathologic diagnosis until the ova were identified.

While a large granuloma was removed surgically, the probability of the infection having spread elsewhere intracranially remains. Interesting was the clinical improvement following stibophen therapy. Whether or not treatment with potassium iodide is helpful in such cases is probably debatable, but it seems a logical procedure in conjunction with administration of stibophen and was used similarly by Vitug, Cruz and Bautista [6] in their second, unconfirmed, case, in which recovery followed such therapy.

Even had the diagnosis of schistosomiasis japonica been made preoperatively, which in the circumstances seems extremely unlikely, it is doubtful whether the usual means of therapy would have caused resolution of the large granuloma encountered, but it may be sufficient to control any remaining tissue infected with the ova.

In view of the recovery in the 2 cases reported by Greenfield and Pritchard,[5] it is believed that a similar course of events can be anticipated in our case. It will be more important, however, to ascertain the patient's condition five or ten years after operation.

Uncommon as schistosomiasis is in this country, because of the large numbers of troops that have been stationed in the Southwest Pacific and infected areas, it is anticipated that the disease will be seen more frequently. In the case of persons with convulsive episodes who have been exposed to endemic areas, the possibility of schistosomiasis should be borne in mind.

SUMMARY AND CONCLUSIONS

An unsuspected and undiagnosed case of schistosomiasis japonica with a large granulomatous tumor in the right occipitoparietal region of the brain, removed surgically with recovery, is reported. Except for previous exposure in the endemic area of Leyte and Mindoro, the patient gave no history or clinical evidence ordinarily encountered in cases of the infection, and operation was performed for an intracranial expanding lesion.

The history, etiology, course and treatment of schistosomiasis japonica are briefly discussed.

Schistosomiasis japonica with cerebral metastases is uncommonly observed; a review of the available literature shows that our case is the third with craniotomy, removal of the intracerebral granuloma and recovery, and the first to be reported in this country. The 2 cases previously reported by Greenfield and Pritchard were strikingly similar to the present one in most respects.

Because of the large numbers of troops that have been stationed in the Southwest Pacific and endemic areas, it is believed that this infection, which has been uncommon in the United States, will be seen more frequently. In persons who have been exposed to endemic areas and have had convulsive attacks, the possibility of schistosomiasis should be borne in mind.

NOTE.—Since this paper went to press, a fourth letter from the patient, written Aug. 8, 1947, has been received. He stated:

". . . As for myself, I feel a lot better than I did while at Hammond or at Ashford. Once in a while my left eye starts bothering me. The pain lasts only about three days at the most. Otherwise, I feel all right. This is about all I can say now but will write again soon."

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PSYCHOSIS DURING WITHDRAWAL OF MORPHINE

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THE PSYCHOSES usually attributed to the use of morphine may be classified as follows: (1) chronic psychosis due to habitual use; (2) psychosis due to withdrawal; (3) psychosis due to idiosyncrasy to the drug.

At the United States Public Health Service Hospital, Lexington, Ky., which is devoted primarily to the treatment of drug addiction, and where this study was made, there has been little experience with the last type (psychosis due to idiosyncrasy), since the patients are addicts and therefore habitually use large doses of morphine. Nevertheless, it is stated that this type of psychosis does occur.[1] It is rare, however, and appears more frequently in women. It is characterized by excitement or delirium. The findings of a previous study [2] indicate that the habitual use of morphine does not cause a chronic psychosis.

The present study is concerned with an evaluation of the second type, psychosis due to withdrawal of morphine. It is generally agreed that many of the psychoses observed during withdrawal of morphine are toxic psychoses consequent to the coincidental use of other drugs, such as alcohol and barbiturates, or scopolamine and atropine, in "cures."[3] However, most authors concur in the opinion that in some instances a psychosis is caused by the withdrawal of morphine alone.[4]

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1. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941. Bastedo, W. A.: Materia Medica, Pharmacology and Therapeutics and Prescription Writing for Students and Practitioners, ed. 3, Philadelphia, W. B. Saunders Company, 1932.

2. Pfeffer, A. Z., and Ruble, D. C.: Chronic Psychoses and Addiction to Morphine, Arch. Neurol. & Psychiat. **56**:665-672 (Dec.) 1946.

3. Noyes, A. P.: Modern Clinical Psychiatry, ed. 2, Philadelphia, W. B. Saunders Company, 1939. Kronfeld, A.: Clinical Interpretation of the So-Called Abstinence Delirium of Morphine Addicts, Jahresk. f. ärztl. Fortbild. **24**:29-38, 1933.

4. Henderson, D. K., and Gillespie, R. D.: Textbook of Psychiatry for Students and Practitioners, ed. 4, New York, Oxford University Press, 1936. Strecker, E. A., and Ebaugh, F. G.: Practical Clinical Psychiatry, ed. 5, Philadelphia, The Blakiston Company, 1940.

PRESENT INVESTIGATION

Of approximately 500 addicts from whom morphine was withdrawn, 12, or 2.4 per cent, were psychotic during the period of withdrawal. The usual procedure of withdrawal consisted in gradual reduction of the dose of morphine sulfate over a ten day period, beginning with administration of ¼ grain (16 mg.) every four hours. Three grains (0.194 Gm.) of phenobarbital was given at 11 a. m. and again at bedtime. Intravenous administration of fluids, flow baths and other supportive therapy were given when indicated. This plan was varied according to the patient's condition. As indicated in the case reports, some of the schizophrenic addicts had abrupt withdrawal of the drug, so that the intensity of the signs of abstinence could be compared with the data of Kolb and Himmelsbach [5] for nonschizophrenic addicts from whom the drug had been withdrawn abruptly.

Each of the 12 patients was carefully examined prior to, during and after withdrawal. Six patients had a chronic psychosis long before withdrawal. Four of these had schizophrenia, and 2 had chronic alcoholic psychosis. Three of the 4 schizophrenic addicts were observed for several months prior to withdrawal of the drug, so that a clear and complete picture of their mental status prior to withdrawal was obtained. The fourth schizophrenic addict had been observed on a previous admission; in addition, he was observed for approximately two weeks

Factors in Psychoses During Withdrawal of Morphine

Psychoses prior to withdrawal		6
Schizophrenia	4	
Alcoholic chronic hallucinosis	1	
Alcoholic deterioration	1	
Drug intoxication during withdrawal		4
Barbiturates	3	
Delirium tremens	1	
Meningoencephalitis, chronic and acute, cause unknown		1
Degenerative encephalopathy and barbiturates		1

prior to withdrawal of the drug. These 4 schizophrenic addicts were observed after withdrawal of the morphine for periods varying from a few months to a year.

Case 1, and the cases which follow, illustrate many of the aspects and observations of this study.

Case 1.—Delirium following abrupt withdrawal of morphine from an addict with paranoid schizophrenia. H., an addict aged 46, had a psychosis diagnosed as schizophrenia at several veterans hospitals during the previous eleven years. The patient was observed for fifty days prior to withdrawal of morphine. The symptoms were those of paranoid schizophrenia. His general behavior was not bizarre. He was attentive and cooperative during interview. He displayed moderately severe anxiety. A poorly systematized delusional system revolving around persecution by the Government was elicited. There were somatic delusions in the form of electric shocks. He claimed that people in the street called him "S. O. B." and "dope fiend," and that the Devil told him, in a voice which he thought was real, to commit sins. He stated that he heard the voice of his dead sister. He was well

5. Kolb, L., and Himmelsbach, C. K.: Clinical Studies of Drug Addiction: Critical Review of Withdrawal Treatments with Method of Evaluating Abstinence Syndromes, Am. J. Psychiat. **94**:759-799, 1938.

oriented as to time, place and person. Calculating ability and recent and remote memory were fair. The Bellevue-Wechsler subtests showed a typical pattern for schizophrenia, and the Rorschach test indicated the disease. On admission, the patient was found to be addicted to the use of unknown amounts of morphine. He was given ½ grain (32 mg.) of morphine sulfate every four hours for fifty days prior to withdrawal of the drug. Withdrawal was abrupt, except for two ½ grain (32 mg.) doses of morphine sulfate given fifty-six and seventy-six hours after withdrawal; this was done because the significant observations had already been made and the patient was uncomfortable. The observations at various intervals after the last dose of morphine are given in the following protocol:

Interval After Last Dose	
24 hr.:	The patient is tremulous, yawning, flushed and restless. He has visual hallucinations of large men and hears them say, "You're going to die; we're going to cut you up." He responds to the voices and says, "No, I'm not going to die." He will not eat because he thinks the food may be poisoned. The affect is notably flattened in relation to the fearful ideas expressed. He is well oriented as to time, place and person.
Interval After First Dose	
31 hr.:	The patient alternately thrashes in bed, asking for morphine, and dozes. He is disoriented as to time and place. The hallucinations are similar to those during the previous observation. The effect remains relatively flattened.
48 hr.:	There are no changes in the condition previously observed.
53 hr.:	Hallucinations are less vivid than before. The patient confabulates. He is oriented in all spheres.
70 hr.:	The condition is unchanged except that there is no confabulation. The picture now is approximately the same as that prior to withdrawal of morphine.
96 hr.:	The condition is unchanged.
8 days:	Auditory hallucinations are now "friendly." They say, "Hey, Jim, are you off that stuff? Get off and stay off."
15 days:	The patient claims that he has had no hallucinations for seven days. There are no further changes.
17 days:	The patient has a "strong feeling" that he will not live. He states that the washbowl is charged with electricity and that it shocked him. He regards this as part of the plan of the government to persecute him. The patient's mental status does not differ from that prior to withdrawal.

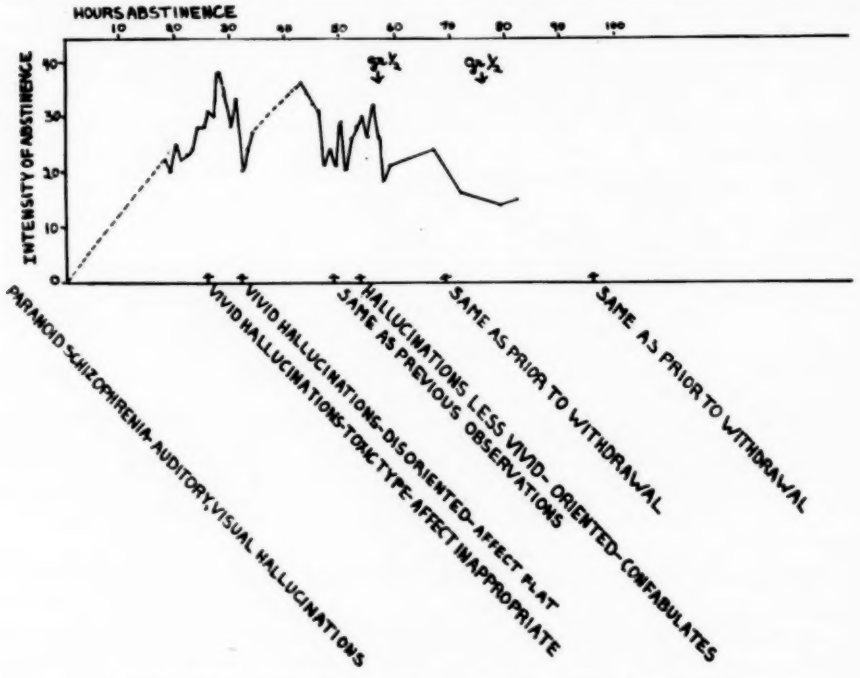
The intensity of the physical signs of withdrawal, based on yawning, lacrimation, rhinorrhea, perspiration, anorexia, goose flesh, dilated pupils, tremor, restlessness and emesis, was evaluated in accordance with the method of Kolb and Himmelsbach.[5] These data are indicated in the graph, with the correlated psychiatric data. In this patient, the signs of withdrawal for the first fifty-six hours did not differ in intensity from those presented by the nonschizophrenic addicts observed by the authors, although the intensity was lower than the average for their group of 65 patients.

CASE 2.—Another addict with paranoid schizophrenia, with an inactive "habit," claimed that an electric current was being used on his mind and that his body had changed in shape. He heard voices call him obscene names, and he was tense and suspicious. He gave this information only after much urging, during several interviews. He was given ¼ grain (16 mg.) of morphine sulfate four times a day, and during the next two weeks this dose was increased to 2 grains (0.13 Gm.) six times a day. This dosage was continued for the next three and one-half months. It was planned to withhold morphine for the entire period of withdrawal; but because the patient had signs of cardiac decompensation at the twenty-third hour he was given ¼ grain (16 mg.) of morphine sulfate, and between the twenty-third and the eighty-first hour a total of 2½ grains (163 mg.) was administered.

The psychiatric changes during withdrawal consisted in a freer expression of abnormal thought content, with surprisingly little increase in anxiety as compared with that to be expected during such a rigorous regimen of withdrawal.

The physical signs of withdrawal were less severe than was expected, and there was a striking absence of sweating; "goose flesh" was constantly present, persisting even during sleep; this sign is usually transient during withdrawal. Approximately one week after the beginning of withdrawal of the drug the psychiatric status was at the prewithdrawal level.

Case 3.—The third addict with paranoid schizophrenia was delusional and hallucinatory prior to withdrawal of the drug. During withdrawal, he expressed the same thought content in a clear sensorium, but the delusions and hallucinations



Mental status correlated with intensity of signs of abstinence.

were more vivid. He became dangerously assaultive because he thought a "dirty machine" was being used on him constantly to effect sexual changes.

Case 4.—The fourth addict had schizophrenia in partial remission. He was seclusive and preoccupied with Yogi philosophy. During withdrawal from the habitual use of a small dose of the drug there was little change in his mental status except for slight increase of anxiety. He gave a history indicative of an acute flare-up of his psychosis, with delusions of persecution and hallucinations, six years previously, during withdrawal from the habitual use of a large dose.

Thus, each of the 3 schizophrenic addicts who had withdrawal of large amounts of morphine showed increased anxiety with increased vividness in their delusions and hallucinations. One of the 3 patients became disoriented.

Summary of Remaining Cases.—A patient with chronic alcoholism who had not been drinking recently, but had experienced frequent episodes of alcoholic hallucinosis in the past twenty years, had vivid hallucinations during withdrawal of morphine, but only at night. His hallucinations were of scooters and fast-moving trains.

A patient who had had chronic alcoholism for forty years and showed changes in memory became greatly confused and disoriented during withdrawal of morphine. Several weeks after withdrawal his mental status returned to the prewithdrawal level, showing changes in memory, but no confusion or disorientation.

From 4 patients barbiturates were withdrawn, in addition to morphine. One had ingested 67 grains (4.35 Gm.) of pentobarbital sodium in the forty-eight hours prior to withdrawal. He became disoriented, had auditory and visual hallucinations of a toxic type and exhibited ataxia, nystagmus and dysarthria. All signs of toxicity, including the psychosis, disappeared ten days after abrupt withdrawal of barbiturates and rapid reduction of morphine over a ten day period.

Another patient, who had used 25 grains (1.63 Gm.) of seconal sodium daily for one year, presented the same symptoms as the previous patient except for the absence of nystagmus, ataxia and dysarthria. The psychosis cleared two weeks after the abrupt withdrawal of barbiturates and the rapid reduction of morphine.

In addition to morphine, 1 addict had used 12 to 18 grains (0.78 to 1.17 Gm.) of sodium amytal daily for a year. On the last night of a ten day period of reduction of the morphine he was delusional and hallucinated. He both heard and saw the devil; he saw elephants and tigers. He said that everyone was talking about him. He feared that he would die. At the time of examination he was well oriented. He was given ¼ grain of morphine sulfate six times a day and additional symptomatic treatment, with immediate decrease of anxiety; but hallucinations did not cease for ten days. In five weeks, during which time morphine was gradually withdrawn, the psychosis cleared entirely. The picture then presented was that of a severe neurasthenic psychoneurosis.

A patient with chronic alcoholism who had used morphine for two years and 1/50 grain (1.3 mg.) of scopolamine hydrobromide daily for eight months, and who had been drinking heavily just prior to withdrawal of the drugs, became restless, tremulous and disoriented. He had hallucinations of monkeys climbing over him and the ringing of bells. The entire picture was similar to that of delirium tremens. According to the patient, even prior to the use of morphine and scopolamine he had had similar episodes after heavy drinking.

A patient with an organic type of psychosis died during withdrawal of the drug, and postmortem examination revealed acute and chronic meningoencephalitis of undetermined cause. An addict with degenerative encephalopathy, probably of vascular origin, which was demonstrated by air encephalography, became confused and disoriented during withdrawal of the drug. Prior to and after withdrawal he had changes in memory and poor calculating ability, but orientation was good.

COMMENT

While it appears that withdrawal of morphine is not sufficient in itself to cause a psychosis, it is apparent that it may intensify the symptoms of a psychosis that already exists; this was demonstrated by the patients who had a psychosis prior to withdrawal. It is interesting that in the case of a schizophrenic addict who had withdrawal of

morphine alone, the increased vividness of the delusions and hallucinations together with the disorientation, resulted in the picture of a toxic psychosis.

It is of course impossible to know how much the withdrawal of morphine contributed to the picture of the toxic psychosis apparently produced by alcoholism and barbiturates; there is little doubt that at least anxiety was increased.

In view of the fact that so large a percentage of persons with addiction to morphine have severe neurotic traits, it is curious that more do not become psychotic during withdrawal of the drug. The withdrawal of morphine, even with the best medical care, is a rigorous, anxiety-producing experience. These facts perhaps lend support to the thesis that the psychoneuroses and the psychoses are not a continuum, but, rather, are distinct entities. The development of delirium in the first schizophrenic addict suggests a close relation between schizophrenia and toxic psychosis.

The findings in this study indicate that withdrawal of morphine, of itself, is rarely, if ever, a cause of psychosis. In each instance complicating factors (schizophrenia and various types of organic psychoses) accounted for the psychosis during withdrawal. It must be noted that rapid withdrawal (ten days) is the method usually employed and that with quicker withdrawal more instances of psychoses would perhaps have occurred. Yet Himmelsbach and Williams [6] found, during the abrupt withdrawal of morphine from 400 addicts under close supervision so that no other drugs could be used, only 1 patient who became obviously psychotic.

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6. Himmelsbach, C. K., and Williams, E. S.: Personal communication to the author.

Abstracts from Current Literature

Physiology and Biochemistry

EFFECT OF COMPOUNDS RELATED TO GLYCOLYSIS IN MUSCLE ON THE SENSITIVITY OF MUSCLE TO ACETYLCHOLINE AND POTASSIUM. CLARA TORDA and HAROLD G. WOLFF, Am. J. Physiol. **145**:419 (Jan.) 1946.

Torda and Wolff studied the effect of products of glycolysis, substances involved in the esterification of carbohydrates and substances inhibiting glycolysis. The effects were studied on the rectus abdominis muscle of frogs and on the acetylcholine and potassium sensitivity of this muscle. Shortening of the muscle was produced by hexose diphosphate, adenosine triphosphate, fluoride citrate and oxalate. Acetylcholine sensitivity of the muscle was increased by hexose diphosphate, pyruvic acid, acetone, acetaldehyde, adenosine triphosphate, creatine phosphate, creatinine, inosinic acid, epinephrine, physostigmine and fluoride. Acetylcholine sensitivity was not altered by dihydroxyacetone monophosphate, β-glycerophosphate, acetylphosphate, propionic acid, acetic acid, acetoacetate, ethyl alcohol, creatine, ammonia, citrate, oxalate, phosphate, pyrophosphate glyceraldehyde or monoiodoacetate. Acetylcholine sensitivity was decreased by high concentrations of butyric acid and by β-hydroxybutyric acid. Potassium sensitivity of the muscle was decreased by Ringer's solution with high calcium content and by potassium-free Ringer's solution, epinephrine, acetaldehyde, and β-hydroxybutyric acid. Potassium sensitivity was not altered by propionic acid, acetone, ethyl alcohol, creatine phosphate, glyceraldehyde or monoiodoacetate. Torda and Wolff could find no direct relation between -SH groups and changes in acetylcholine and potassium sensitivity of muscle. The authors conclude that lowering of the calcium ion content of muscle increases potassium sensitivity and induces shortening of the muscle, and that changes in intracellular adenosine triphosphate increase acetylcholine sensitivity.

FORSTER, Philadelphia.

THE INFLUENCE OF AVOIDANCE CONDITIONING OF THE COURSE OF NON-AVOIDANCE CONDITIONING IN DOGS. G. B. WHATMORE, E. A. MORGAN and N. KLEITMAN, Am. J. Physiol. **145**:432 (Jan.) 1946.

Whatmore, Morgan and Kleitman found that, while the avoidance and the nonavoidance type of conditioning procedure can be used separately to develop and maintain conditioning of leg flexion performance in dogs at a high level, if the two types of conditioning are used concurrently in the same animal the avoidance conditioning has a strong deleterious effect on the course of the nonavoidance conditioning but is itself fully retained.

FORSTER, Philadelphia.

THE PERIPHERAL VISUAL ACUITY OF 100 SUBJECTS UNDER SCOTOPIC CONDITIONS. FRANK N. LOW, Am. J. Physiol. **146**:21 (April) 1946.

Low studied the simple visual acuity for form of 100 subjects under scotopic conditions. Fourteen points on the retinal periphery were studied. Simple form acuity under scotopic conditions is somewhat weaker than is photopic acuity in the same retinal areas. Acuity isopters for night vision are nearly circular, being flattened only on the top. This is in sharp contrast with the irregular oval isopters known for day vision. The dispersion of scores is less in scotopic than in photopic acuity. Impairment. of the scotopic mechanism can prevent successful measurement with this technic. Low found that the technic under scotopic conditions is less reliable than the same technic under photopic conditions.

FORSTER, Philadelphia.

EFFECT OF EXTIRPATION OF PARASTRIATE CORTEX ON LEARNED VISUAL DISCRIMINATIONS IN MONKEYS. HARLOW W. ADES, J. Neuropath. & Exper. Neurol. **5**:60 (Jan.) 1946.

Three monkeys were trained to discriminate between pairs of visual stimuli which varied with respect to size, shape and color. It was observed that monkeys so trained lose the power of this type of discrimination if areas 18 and 19 are destroyed bilaterally in one stage. The discrimination can then be relearned postoperatively at approximately the same rate as originally. If the cortical destruction is carried out in two stages with an interval between during which testing is continued, the discriminatory ability is lost. GUTTMAN, Philadelphia.

THE PYRAMIDAL TRACT: THE REPRESENTATION OF THE LATERAL CORTICOSPINAL COMPONENT IN THE SPINAL CORD OF THE CAT. A. M. LASSEK, J. Neuropath. & Exper. Neurol. **5**:72 (Jan.) 1946.

Utilizing a silver stain, Lassek reports on the number of pyramidal fibers descending into the spinal cord of the cat.

Massive cortical lesions on the left side were made in a series of 8 neurologically mature cats so that the cells of origin of the pyramidal tract were completely, or almost completely, ablated. The animals were then killed at intervals of three, six, twenty-six, sixty-eight, one hundred and sixty-eight, one hundred and eighty, two hundred and fifty-four and two hundred and seventy-four days after operation. In the last 2 animals, a second, similar, operation was performed on the opposite hemisphere about thirty days preceding the date of killing. The bilaterally decorticated animals gave an opportunity to compare the effects of acute and chronic lesions, to study any possible displacement of nonpyramidal fibers into the pyramidal area and to determine the status, to some extent, of the homolateral tract.

Representative sections from the mesencephalon, pons, medulla and four regions of the spinal cord were stained either with the protein silver or the Bodian technic, mostly with the former. At all levels, the degenerated portion of the pyramidal tract on the side of the unilateral lesions was compared with the pyramidal tract in the normal, unaffected, half. Both silver methods are suitable for tracing degenerated axons, but the protein silver technic was found to be preferable in the author's hands. In the more acute stages, analysis is largely subtractive. As the glial tissue proliferates, the degenerated area becomes darker and can be more easily followed. Lassek observed that few, if any, fibers of the crossed pyramidal tract extend the entire length of the spinal cord in the cat. The tract terminates largely in the upper two thirds of the spinal cord. There is evidence that many of its fibers terminate high in the cervical region of the cord. Many fibers are normally present in the pyramidal area of the cord which do not belong to any part of the pyramidal system, including the so-called homolateral corticospinal component. Degeneration of axons of the pyramidal tract in the cat was detected as early as three days with the protein silver method of staining. Cellular activity of the supporting elements continues for nine months or more in the pyramids after massive cortical ablation. In its phylogenetic development the pyramidal tract in the cat appears to occupy a position intermediate between the lower mammals and man.

GUTTMAN, Philadelphia.

A NOTE ON A MECHANISM OF ARTERIAL RUPTURE IN CEREBRAL ARTERIOSCLEROSIS. WILLIAM J. TURNER, J. Neuropath. & Exper. Neurol. **5**:168 (April) 1946.

The breaking of an inelastic substance subjected to repeated flexion may account for cerebral vascular aneurysm and rupture with cerebral arteriosclerosis, particularly when complicated by hypertension. A mechanism of this sort has not hitherto been considered.

It is well known that in arteriosclerosis the arteries become longer and more tortuous, as well as more inelastic; also, with each pulsation the arteries tend to straighten but are unable to do so because they are fixed at their points of bifurcation. It seemed possible that the combination of these factors might result in a tendency of the arterial wall to rupture near a point of bifurcation of the artery and that this tendency might be aggravated by an elevation of blood pressure.

A simple ingenious mechanical setup is described in detail. This arrangement allows for a sudden dilation of the longer of two rubber tubes. By careful regulation of the pressure, dilatation can be repeatedly developed, with eventual formation of a lax and dilated wall of the tubing prior to its final rupture. If the pressure is too greatly elevated or is maintained too long at a high level, the rupture occurs suddenly and without warning. A number of variants of the model described yielded results in accord with the foregoing statement. The more tortuous the course of the rubber tube, almost regardless of its length, the earlier will the rupture occur, and the more certainly at the distal point of fixation. In more than forty experiments the straight tube did not once rupture.

GUTTMAN, Philadelphia.

EFFECT ON THE ELECTROENCEPHALOGRAM OF LOCALIZED PRESSURE ON THE BRAIN. MARK ALBERT GLASER and HENDRIKUS SJAARDEMA, J. Neurophysiol. **9**:63 (March) 1946.

Glaser and Sjaardema describe a method for producing localized increased intracranial pressure. The apparatus consists of a lucite rod 0.713 cm. in diameter attached to a micrometer screw. Introduction of the lucite rod through the trephined skull produced increased intracranial pressure. The electrical activity of the cortex was recorded before, during and after the introduction of increased intracranial pressure. Glaser and Sjaardema found that slowly increasing the intracranial pressure produced alterations in the electroencephalographic pattern. These alterations included a high incidence of activity analogous to that seen in clinical and experimental epilepsy.

FORSTER, Philadelphia.

EYE MOVEMENTS FOLLOWING STRYCHNINIZATION OF THE SUPERIOR COLLICULUS OF CATS. JULIA T. APTER, J. Neurophysiol. **9**:73 (March) 1946.

Apter found that strychninization of a small area of the superior colliculus of the cat activated the path of reflex attraction of the eyes toward a light in the peripheral visual field. Each point on the superior colliculus was found to regulate movement of the eyes to a particular part of the visual field, thus, medial points caused upward and lateral movements, while lateral points caused lateral downward movements. Each colliculus was concerned with movements to the contralateral visual fields. Conjugate movements of the eyes were found to be due to contraction of agonist and relaxation of antagonist muscles, and this regulation was mediated by the superior colliculus. Charting of the superior colliculus for control of localized ocular movements correlated for projection of the visual field on the colliculus.

FORSTER, Philadelphia.

SPINAL CONDITIONING IN DOGS. W. N. KELLOGG, N. H. PRONKO and JAMES DEESE, Science **103**:49 (Jan. 11) 1946.

There is evidence in the literature that learning—or what appears to be learning of a rudimentary sort—can occur in the caudal extremities of higher vertebrates after the spinal cord has been completely transected. These observations were originally made on acute spinal dogs. If these observations could be confirmed and elaborated on, it would seem that the organism, or a fragmentary part of it, can form simple associations without the aid of the cerebrum or any of the higher centers of the central nervous system and that these centers are, therefore, unneces-

sary for the occurrence of learning of the sort indicated. The authors attempted conditioned reflex training with chronic spinal dogs.

The conditioned stimulus in the present experiments was an electric shock to the left rear foot, and the unconditioned stimulus was a shock to the right rear foot. The response to be conditioned was the moving or flexing of the entire right hindlimb. Each of the subjects was given 1,000 conditioning trials in groups of 100 trials each, spaced on alternate days over a period of about three weeks. Despite the differences in experimental technic in the two investigations, there was clear evidence in both the acute and the chronic preparations that a muscle twitch or an instantaneous jerk of the right rear leg could be evoked by the conditioned stimulus to the left rear foot. The twitch response was small in amplitude and of very short latency. The twitching movement of the right rear member may be the same as the spinal conditioned response observed in the acute preparation by Shurrager and Culler.

The twitch response observed in the chronic spinal animals, however, was only a part of the behavior elicited by the conditioned stimulus. Records of movement of the right hindlimb also disclosed a second, and conflicting, type of reaction. In place of the muscle twitch or incipient flexion, there often occurred an extension of the right rear limb, i. e., the crossed extension reflex. Although the extension response was initiated immediately by the conditioned shock, it usually lasted from two to three seconds. With respect to duration it had no resemblance, therefore, to the very brief jerk of the flexing muscles.

The two sorts of reflex movements were antagonistic and mutually inhibitory. They never occurred together on the same trial. One response usually predominated for several trials and was then superseded by the other. Yet there can be no doubt that both responses were genuine and that they were unstable, appearing and disappearing, even though the stimulating conditions remained the same.

Frequency graphs of the flexing twitch, as well as of the extension response, were so irregular that they were quite unrecognizable as learning curves. The only similarity to the typical curve of learning was that each response was absent at the start of training and increased somewhat in frequency during the later trials. When both the crossed extension and the flexion reaction were considered together, the combined frequency of responsiveness for all animals rose gradually for the first three hundred trials and continued at approximately 20 per cent for the remaining 700 trials.

In spite of this irregular level of about 20 per cent, which persisted when the frequencies of the two responses for all subjects were pooled, no evidence of retention was observed over the intervals between experimental sessions in the behavior of any one dog considered by itself. The spinal behavior of the present subjects cannot satisfactorily be fitted into the conditioning formula, since that behavior was a combination of two antagonistic responses, now one occurring, now the other.

GUTTMAN, Philadelphia.

THE EPIDEMIOLOGY OF THE 1945 OUTBREAK OF POLIOMYELITIS IN MAURITIUS. ALLAN M. MCFARLAN, Proc. Roy. Soc. Med. **39**:323 (April) 1946.

In February 1945, in Mauritius, after a cyclone which caused widespread damage to dwellings, there occurred intestinal diseases in increasing prevalence and an epidemic of poliomyelitis. During the first five months of 1945 there were at least 1,018 cases of the disease, with a rate of attack of 2.4 per 1,000 of population. Of 851 cases in one series, 64 per cent were of children under the age of 5 years and 95 per cent of children under the age of 10 years. No definite paralysis was present in 4 per cent of the cases, whereas in 86 per cent the legs were affected. A symmetric, somewhat steep curve, resembling that of an influenza epidemic, characterized the weekly incidence of cases and suggested an infection with a very short incubation period and a high degree of infectivity, unlike typical paralytic

poliomyelitis. Such a curve might apply to a carrier epidemic of the virus. Because casual contact apparently sufficed to transmit infection, the author concludes that the presence of the virus in the pharynx may be more important for the spread of infection than its presence in the feces.

The outbreak, first localized in one area, spread rapidly throughout the island, apparently in a number of instances carried by healthy adult men. Except for one village, where contamination of ice cream possibly played a part in the spread of the disease, the type of epidemic suggested a spread by transient carriers. Contact was the most important factor determining infection.

BERRY, Philadelphia.

EFFECT OF PENICILLIN ON REGENERATION OF NERVES: PRELIMINARY NOTE. O. AIDAR and C. MIGNONE, Arq. de neuro-psiquiat. **3**:246 (Sept.) 1945.

The tibial nerve was sectioned in 32 rabbits. In 16 rabbits the site of the experimental lesion was contaminated with Staphylococcus aureus. In the other 16 no such organisms were introduced. Each group of 16 rabbits was then divided into two subgroups of 8 each. One cubic centimeter of penicillin (200 to 250 Oxford units) was placed at the operative site. The penicillin had no effect on the regeneration of nerves whether infection was present or not.

N. SAVITSKY, New York.

Neuropathology

NEUROPATHOLOGIC STUDY OF ACUTE HUMAN POLIOMYELITIS, WITH SPECIAL REFERENCE TO INITIAL LESION AND TO VARIOUS POTENTIAL PORTALS OF ENTRY. H. K. FABER and ROSALIE J. SILVERBERG, J. Exper. Med. **83**:329 (April) 1946.

Faber and Silverberg examined the tissue of the peripheral and central nervous systems of 8 patients who died of acute poliomyelitis. On the basis of concurrent lesions in the primary and secondary centers, the involvement of the various systems was found to be (*a*) very frequent for the trigeminal afferent system (fifth cranial nerve), (*b*) fairly common for the visceral afferent system (ninth and tenth cranial nerves) but less than for the fifth, (*c*) occasional for the gustatory system (seventh, ninth and tenth cranial nerves), (*d*) occasional for the upper levels of the sympathetic system (pharynx, bronchial tree, upper part of the esophagus) and (*e*) occasional or doubtful for the lower sympathetic system (intestine). The probability of their having acted as primary pathways for entering infection was in direct correspondence with the frequency of involvement. The vagal efferent (parasympathetic) system (tenth cranial nerve) and olfactory (first cranial nerve) system were not involved. The evidence of penetration through the upper alimentary and respiratory tracts was more conspicuous and consistent than that of penetration through the lower alimentary tract. The pharnyx appears to be an especially favorable site for the primary penetration of virus into the body.

J. A. M. A.

THE PATHOLOGY OF INJURY TO NERVE INDUCED BY COLD. D. DENNY-BROWN, RAYMOND D. ADAMS, CHARLES BRENNER and MARGARET M. DOHERTY, J. Neuropath. & Exper. Neurol. **4**:305 (Oct.) 1945.

The authors record the results of two series of experiments, both of which were carried out on cats. In the first series, the sciatic nerve was exposed aseptically and a length of 1 cm. packed off and frozen solid by a spray of carbon dioxide. After a variable interval of time the frozen part of the nerve was then thawed by the application of cool or tepid isotonic solution of sodium chloride. On the day after the operation and thereafter the animals were examined to determine the degree of motor and sensory paralysis. Weakness or paralysis of the dorsiflexors

and plantar flexors of the foot and spreading of the toes could be detected by watching the animal walk and by testing the placing reaction. Loss of touch and pain sensations could be judged by response to contact and pinching of the paw. When the animals were killed, motor responses to faradic current applied above and below the lesion were noted. The nerves were stained by a variety of histologic methods, chiefly stains for myelin (Spielmeyer), fat (oil red O) and axis-cylinders (Gros-Bielschowsky) and general tissue stains.

In the second series, cooled brine at a constant temperature, ranging from —4.0 to + 3.0 C. in the various experiments, was circulated through a small cylindric metal jacket surrounding a segment of sciatic nerve (20 mm.) for a measured period of time (usually two hours). The temperature of the brine was measured by thermometer at the inflow and the outflow and the temperature of the interior of the nerve by a fine thermocouple (copper-constantan) inserted between the fasciculi of the nerve. The vessels supplying the nerve were always left intact, and the entire procedure was carried out aseptically. Care was also taken to avoid kinking of the nerve. As in the first series, the animals were killed after varying periods of survival and observation and the nerves examined microscopically after suitable fixation and staining.

In addition, a few experiments were carried out in which the shaved, oiled ear of an anesthetized rabbit was transilluminated and observed in a transparent glass chamber containing circulating, cooled brine (—1.0 to —4.0 C.). However, after immersion of the ear for one hour at —4 C. there was no resultant loss of sensitivity to pinch, and since vessels of capillary size could not be satisfactorily observed these experiments were abandoned.

The observations indicate that myelin and axis-cylinders of mammalian peripheral nerve are selectively damaged by exposure to cold, the largest fibers being the most sensitive and the smallest the least sensitive. Damage to large motor fibers and nerves conveying sense of contact is caused by exposures to such temperatures as + 8.0 C. for intervals as short as thirty minutes. The mildest degree of damage resembles that produced by transient ischemia, but the complete lesion results in the complete destruction of the myelin of the affected fibers without necessarily damaging that of smaller fibers. The demyelinated segment of the axon-cylinder degenerates. The affected myelin undergoes dissolution, and necrosis of whole nerve bundles occurs only after freezing. Regeneration is rapid and complete in all grades of the injury short of complete necrosis.

GUTTMAN, Philadelphia.

ACUTE MYELITIS: A CLINICAL-PATHOLOGIC STUDY. GEORGE B. HASSIN and SAMUEL B. BRODER, J. Neuropath. & Exper. Neurol. **5**:106 (April) 1946.

Hassin and Broder report the case of a middle-aged man, in apparent good health, who shortly after an infection of the upper respiratory tract experienced paraparesis of the lower extremities, from which he improved and was able to resume his work. About six weeks later paraplegia suddenly set in, associated with complete anesthesia up to the level of the eighth thoracic segment and loss of deep, superficial and sphincteric reflexes. No spinal block could be demonstrated. The spinal fluid was turbid and contained 60 mg. of total protein per hundred cubic centimeters. In spite of the repeated clinical and laboratory studies, a definite diagnosis could not be arrived at, even after a laminectomy had been performed.

Postmortem examination, done about twelve hours after death, revealed that the spinal cord was covered at the lower dorsal level with a slightly gray exudate. The blood vessels in the middorsal region of the cord were dilated and in some places appeared thrombosed.

The pathologic diagnosis may be summed up as inflammation, degeneration, necrosis, meningitis and radiculitis, all confined to the spinal cord. Though diffuse, the changes were especially pronounced in the thoracic region and, as a rule, involved the white substance more than the gray, where circumscribed foci of softening were also present, with the complete preservation, however, of the

ganglion cells and the blood vessels. These showed only infiltrations, either with hematogenous elements or with compound granular corpuscles (gitter cells).

Hassin and Broder state that acute myelitis should be considered among the commonest causes of acute paraplegia. In acute myelitis both the gray and the white substance of the spinal cord are affected by an inflammatory process. These changes may be immense or be replaced by the process of softening or necrosis, with which they may be combined. The phenomena of inflammation, softening and necrosis, as observed in cases of acute myelitis, are to be considered mere gradations of one toxic-infectious disease process. The rest of the central nervous system, the brain, for instance, reacts by exhibiting proliferative vascular changes, which are those of productive encephalitis.

GUTTMAN, Philadelphia.

THE CEREBRAL CORTEX IN THE VERY OLD HUMAN BRAIN. W. RIESE, J. Neuropath. & Exper. Neurol. **5**:160 (April) 1946.

This study of the chronologically very old brain was undertaken in order to answer the following question: Are the changes to be seen in the very old brain commensurate with the age of the patient or the length of the clinical course? Rothschild stated a few years ago that he observed no parallelism between the severity of the parenchymatous changes in the brain and the age of the patient. To date, no attention has been paid to the question of the length of the clinical course.

The material was obtained from 18 patients, aged from 77 to 107 years. All were inmates of a state hospital, and all but 5 had had senile dementia of eleven months' to fourteen years' duration. For 4 patients the diagnosis of "psychosis with cerebral arteriosclerosis" was made; the fifth, a 90 year old woman, who was admitted at the age of 55 to the state hospital with the diagnosis of "involutional melancholia," had never exhibited the senile type of psychosis. In some instances the exact onset of the disease could not be determined; in others a more or less sudden deterioration took place after a slow initial onset. The microscopic studies were made on sections prepared by the Nissl method.

It was observed that the overwhelming majority of very old brains showed at least some cortical atrophy, diffuse or regional in distribution. The degree of cortical atrophy was not necessarily proportionate to the age of the patient. The cytoarchitecture was surprisingly well preserved in the very old brains, the three types of pyramidization, granularization and spindlization being as obvious in these brains as in the brains of young and adult persons. Cellular changes were consistently present in the very old brains, but these were not proportionate to the age of the patient. Neither the degree of cortical atrophy nor the extent of cellular destruction was proportionate to the duration of the clinical history.

GUTTMAN, Philadelphia.

BILATERALLY SYMMETRIC SYMPATHICOBLASTOMA. MOSTO, RODAS and DANTE, Prensa med. argent. **33**:277 (Feb.) 1946.

Bilaterally symmetric tumors were observed in the region of the adrenal glands in a man aged 52. He had complained of severe pain in the lumbar region with radiation anteriorly for about six months. There had been considerable loss in weight during this period. An abdominal tumor was palpated. There was roentgenographic evidence of a tumor in the upper and anterior part of the mediastinum. Perirenal insufflation of air was not done. An exploratory abdominal operation revealed the tumors to be of about the same size, 15 by 20 by 12 cm. The kidneys were adherent to the tumors. There were metastases to the lungs and mediastinum. Histologic examination indicated that the tumor arose from the cells of the sympathetic nervous system.

N. SAVITSKY, New York.

CEREBRAL METASTASIS COMPLICATING PRIMARY CANCER OF THE LUNG. I. M. HERNANDEZ and LOUIS IRIGOYEN, Publ. d. Centro de invest. fisiol. **9**:77 (June) 1945.

Four cases of cerebral metastases were found in 50 cases of primary tumor of the lung (8 per cent). In 3 cases the metastases to the brain were multiple. At times the cerebral changes resulting from the metastases dominated the picture. In all the cases pulmonary symptoms were present before cerebral complications appeared. The authors believe that metastases to the brain take place through the blood stream directly into the lesser circulation, most frequently into the middle cerebral artery. In 1 case there were multiple metastases to the cerebrum and the cerebellum.

N. SAVITSKY, New York.

Meninges and Blood Vessels

MENINGITIS AND ABSCESS OF THE BRAIN DUE TO PANSINUSITIS. LAWRENCE T. CACIOPPO, Arch. Otolaryng. **42**:47 (July) 1945.

The use of drugs, especially penicillin, has considerably improved the outlook for patients having infections of the paranasal sinuses complicated by intracranial extension. There are occasions, however, when these drugs may greatly improve the clinical picture and at the same time mask the signs of extension of the pathologic process.

Cacioppo reports the case of a man aged 33, known to have diabetes, who was admitted to the hospital complaining of headache in the left frontal region of ten days' duration. There were edema and tenderness over the left side of the forehead. The patient had chronic sinusitis with involvement of the antrum and a fistula draining into the left upper premolar region. Further examination corroborated a diagnosis of acute pansinusitis of the left side and diabetes mellitus. Sulfadiazine therapy was begun at once, and insulin was ordered. Some improvement was noted the next day, although there was definite drainage from the left frontal region. On the fourth day after his admission to the hospital, a Killian operation was done and a drainage tube inserted into the left frontal sinus. Two days after this operation meningitis developed. The cell count of the spinal fluid was 11,000 per cubic millimeter, and Babinski and Kernig signs and nuchal rigidity were present. Penicillin therapy was started, and by the eighth day the temperature had dropped from 104 to 99 F. On this day bilateral bronchopneumonia was found, though the general picture of meningitis seemed improved. On the twelfth day the patient showed signs of irritation of the left frontal lobe. The bronchopneumonia showed complete resolution; there was improvement in the meningitis, the spinal fluid cell count and the neurologic signs after a month of hospitalization, though a roentgenogram showed osteomyelitis of the frontal bone. By the end of the fifth week the patient had vomiting, headache, weakness of the right upper and lower extremities and paralysis of the right side of the face. An intracranial exploration was done, but the patient became comatose and died forty-eight hours later. Autopsy showed an acute abscess of the brain in the occipital lobe and a subdural abscess in the frontal region. Since there was no apparent communication between the two abscesses, extension was probably by way of the subdural space from the subdural abscess to the occipital lobe and thence forward. Uncontrolled diabetes added complications in this case.

RYAN, Philadelphia.

Diseases of the Brain

FIBROSARCOMA OF THE SPHENOID BONE, PRODUCING THE SYNDROME OF THE LATERAL WALL OF THE CAVERNOUS SINUS. MAX GOLDMAN and RAYMOND D. ADAMS, J. Neuropath. & Exper. Neurol. **5**:155 (April) 1946.

Fibrosarcoma of the cranium is rare. Goldman and Adams report this case because of the infrequency and unusual character of the clinical syndrome produced by encroachment on the cavernous sinus.

In this case, that of a middle-aged white man, the neurologic status was complicated by jaundice, fever and chills, which were attributed to dysfunction of the gallbladder. In the middle of June the patient experienced diplopia and discomfort in the right frontotemporal region. There were ptosis of the right eyelid and paresis of the right superior rectus muscle. Within five days the paresis progressed to complete ophthalmoplegia, and on the sixth day the pupil had become dilated and fixed to light and in convergence. The corneal reflexes remained active; there was no sensory impairment over the face, and proptosis could not be detected by inspection. The optic fundi, visual acuity and visual fields were normal. Olfactory function was preserved. No other neurologic abnormalities were observed. The heart and lungs were normal. No abdominal masses or viscera were palpable. The lymph nodes were not enlarged. Roentgenograms of the base of the skull revealed no bony defects. Roentgenograms of other bones, similarly, showed no abnormality. The blood counts and studies of the cerebrospinal fluid all gave results within the limits of normal. The blood phosphatase level and the sedimentation rates were not increased.

A month later the discomfort in the forehead became intense and almost constant. About two months after onset of the neurologic symptoms and signs, examination revealed no change in his status. The patient became confused and comatose and died.

Postmortem examination revealed a mass of grayish red tissue presenting just lateral to the sella turcica on the right side. This tissue was attached to the outer surface of the dura mater and bulged into the anteromedial part of the middle fossa, and in so doing it displaced the cavernous sinus laterally. Coronal sections of the sphenoid bone revealed the full extent of the tumor. The body of the sphenoid bone was largely replaced by tumor tissue, which had extended into and filled the sphenoid sinus. The right cavernous sinus was obliterated by the lateral extension of the tumor. In cross section, the third, fourth, ophthalmic fifth and sixth cranial nerves on the right side were unusually cellular, there being an increase in both Schwann cells and fibroblasts. The anatomic diagnosis was fibrosarcoma of the sphenoid bone with extension into the sphenoid and cavernous sinuses.

This case indicates the difficulty in differential diagnosis between a lesion in the cavernous sinus and one in the sphenoidal fissure. It is frequently stated that proptosis and orbital edema are more commonly found when the cavernous sinus is involved. However, in this case these ophthalmic signs were not observed, even though the sinus was almost obliterated at the time of necropsy. Other helpful points in the diagnosis of lesions of the cavernous sinus are involvement of the maxillary division of the trigeminal nerve, which leaves the skull through the foramen rotundum rather than the sphenoidal fissure, and roentgenographic evidence of destruction of adjacent bony structures. When the sphenoidal fissure is the site of the pathologic process, proper roentgenograms of the orbit may show widening of the fissure or destruction of its wall.

GUTTMAN, Philadelphia.

ISOLATION OF ST. LOUIS ENCEPHALITIS VIRUS FROM PERIPHERAL BLOOD OF HUMAN SUBJECT. R. J. BLATTNER and FLORENCE M. HEYS, J. Pediat. **28**:401 (April) 1946.

Blattner and Heys isolated a filtrable virus from the blood of a boy aged 8 years whose clinical manifestations were suggestive of a virus infection with minimal involvement of the central nervous system. The virus persisted in the peripheral blood approximately four days after onset of clinical symptoms. With the newly isolated strain of virus, parallel serum-virus neutralization tests were performed with blood serums obtained from the patient during the clinical course and with serums of rabbits immunized against a known St. Louis encephalitis strain of virus (Hubbard). Controls consisted of mixtures with broth alone and with normal human serum. The results of these tests showed that the infectious agent isolated is neutralized by the serum of a rabbit immunized to the known strain (Hubbard)

of the St. Louis encephalitis virus. During the clinical course the patient formed increasing antibody titer to the newly isolated virus and to known St. Louis encephalitis virus (Hubbard). Two criteria for the diagnosis of a virus disease have been satisfied, namely, isolation of an infectious agent from the patient and development during the course of clinical illness of type-specific humoral antibodies.

J. A. M. A.

CEREBRAL PALSY. E. STANLEY EVANS, Proc. Roy. Soc. Med. **39**:317 (April) 1946.

The rationale of treatment of patients admitted in the past three years to the Cerebral Palsy Unit at Queen Mary's Hospital, Carshalton, England, was founded on the principles originally laid down by Little and enunciated by Dr. Winthrop Phelps, of Baltimore, in his remedial school for spastic patients. These principles rest on the following basis: (1) an accurate diagnosis of the condition, i. e., whether the spasticity results from a lesion of the cerebral cortex, the underlying phenomenon being the spastic stretch reflex, or whether the cause lies in a tension athetosis, the tension representing a secondary result of an attempt to control the athetosis; (2) a careful mental assessment, to estimate the ability of the child to respond to teaching and training (less than 10 per cent of the athetoid children, but over 60 per cent of the spastic children, were found ineducable), and (3) a comprehensive, intensive and individually oriented therapeutic approach.

The obvious purpose of treatment is twofold: to estimate economic potentiality and to make the child independent, or at least semi-independent. Spastic patients are retrained by graded exercises until the spastic muscles can be utilized without the development of the spastic stretch reflex and improved tone of the weak muscles is attained. Resort to operation is made only when structural contractures are present.

Jacobsen's methods of conscious and voluntary relaxation are utilized to assist the athetotic patient in eliminating purposeless movements.

With the focus on individual training, besides the medical staff, a physical therapeutist, an occupational therapeutist, a speech trainer, an educational psychologist and a school teacher discuss the individual patients at weekly conferences.

Of 50 patients with cerebral palsy seen within the past few months, 32 were found to be educable. The results have far exceeded the author's expectation.

BERRY, Philadelphia.

Diseases of the Spinal Cord

MYELITIS FROM MUMPS. R. LIGHTWOOD, Brit. M. J. **1**:484 (March 30) 1946.

Lightwood reports a case of "local paralysis" resulting from mumps in a 16 year old youth. The clinical picture so strongly resembled poliomyelitis that this diagnosis would probably have been made were it not for the obvious evidence of mumps. The patient made an early and complete recovery.

ECHOLS, New Orleans.

ACTINOMYCOSIS OF THE THORACIC VERTEBRAE WITH PACHYMENINGITIS AND COMPRESSION OF THE CORD. LAMARTINE DE ASSIS and MIGNONE, Arq. de neuro-psiquiat. **4**:21 (March) 1946.

A man aged 52 had been ill for two and a half years. The onset was insidious, with infected cervical glands, which broke down soon after the illness began. Increasingly severe backache soon appeared. The pain was dorsal and apparently radicular for about ten months, being worse with coughing and sneezing. During this time there were also progressive weakness in the lower limbs, occasional coughing and hemoptysis. The cutaneous lesions spread to the thorax. Examination on his admission to the hospital showed evidence of discharging lesions of the

skin, pulmonary infiltration, dorsal kyphosis and painful and enlarged liver. The spleen could be percussed easily. The blood pressure was 110 systolic and 70 diastolic. There was weakness of the lower limbs with exaggeration of the tendon reflexes and a bilateral Babinski sign; there were no sphincteric disturbances. The sensory examination was not reliable because of the patient's condition. Actinomyces were isolated from the discharging cutaneous lesions. Roentgenograms showed pulmonary infiltration and extensive destruction of the dorsal vertebrae. The spinal fluid was xanthochromic with no manometric block. Injection of iodized poppyseed oil revealed partial block with diffuse arrest of droplets, indicating the probable existence of leptomeningeal adhesions. Autopsy showed extensive actinomycosis of the lungs with purulent exudate in the soft tissues around the spinal column and in the bones. There was extensive thickening of the dura mater with scattered spots of inflammatory exudate. The spinal cord was intact. The pachymeningitis caused a myeloradicular syndrome without actual involvement of the cord. The authors report this complication as the first of its type in the Brazilian literature.

N. Savitsky, New York.

Surgical Treatment of Refractory Sciatica Due to Herniated Disk. A. Garcia Frugoni, Rev. Asoc. méd. argent. **59**:763 (July 15) 1945.

The author's observations are based on 35 cases of verified herniated disk and 7 cases of tumor of the cauda equina. In most cases the herniated disk was between the fourth and the fifth lumbar vertebra or between the fifth lumbar and the first sacral vertebra. The author favors a complete laminectomy, with wide and clear visualization of the operative field. When the dura is opened, bulging in the anterior part of the operative field is observed. A small incision at the site of this bulge usually localizes the disk. The articular facets were spared in all cases. There was no impairment of motion of the spine in any of the cases; no orthopedic measures were necessary to reenforce the spine. All the patients returned to work and were able to continue without reduction of efficiency. The author recommends always cutting the affected root in order to minimize the possibility of recurrence of radicular pain. The root is usually observed to be enlarged, edematous and congested and is sometimes covered with fine exudate. Because of overlapping of root segments, sensory sequelae do not persist after rhizotomy. Garcia Frugoni recommends the intrathecal injection of contrast medium in order to demonstrate and localize the herniated disk.

N. Savitsky, New York.

Peripheral and Cranial Nerves

Disturbed Vestibular Function. Marvin F. Jones, Arch. Otolaryng. **41**:272 (April) 1945.

The symptoms of vestibular irritation listed in the literature are nystagmus, vertigo and ataxia. There are approximately thirty-five known causes of these symptoms. Vestibular irritation may be due to nonsuppurative involvement of the labyrinth or to infection, local or general. Pus inside the labyrinth prevents any response to stimulation. A labyrinth surrounded by pus or secondarily involved in an inflammatory process will still respond to stimuli. The author was successful in curing many patients of their labyrinthine symptoms by removing the infected cells surrounding the labyrinth, using the postauricular incision for radical mastoidectomy. In other patients better results were obtained by using an endaural approach to the cells.

Jones reports on 3 patients who were not cured of their symptoms. The first was a man aged 48 who had right-sided facial paralysis for two years before roentgenograms were made, revealing extensive absorption of the petrous ridge from the labyrinth to the apex and absence of the lower half of the mastoid cells.

Five years later, he had exacerbation of his chronic mastoiditis, and an endaural exploratory operation was performed. Extensive destruction of bone and a nerve defect in the facial nerve were encountered. The patient did not respond well until sulfadiazine was administered into the spinal fluid and the wound packed with sulfathiazole paste. He finally recovered but still had paralysis of the right vocal cord, hoarseness and facial paralysis. The second case was that of a woman who, after several attacks of acute otitis media over a period of years, had had a discharging ear, vertigo and tinnitus for thirteen years. She had impaired hearing in the right ear and complained of falling to the right. An endaural mastoidectomy revealed a pathologic exposure of the dura of the middle fossa, exposure of the facial nerve and necrosis of the labyrinthine wall with exposure of the membranous labyrinth. She improved for several months but had a recurrence of her symptoms. It was then believed that the osseous lesion was tuberculous, in view of the fact that the patient had a pulmonary lesion which was arrested several years earlier. The third case was that of a man who showed symptoms of petrositis and labyrinthine involvement. Endaural removal of the perilabyrinthine cells relieved his symptoms, but they recurred.

The author believes that removal of perilabyrinthine cells should be attempted to relieve symptoms indicating inflammatory labyrinthine involvement other than diffuse suppurative labyrinthitis before the labyrinth itself is operated on.

RYAN, Philadelphia.

LABYRINTHITIS FOLLOWING PURULENT INFECTION OF THE MIDDLE EAR. FRANZ ALTMANN and JULES G. WALTNER, Arch. Otolaryng. **42**:93 (Aug.) 1945.

A thorough knowledge of the genesis of labyrinthitis, as an aid in the prevention of hearing defects due to labyrinthine infection, is still desirable in spite of recent chemotherapeutic advances. Detailed histopathologic studies of many cases have shed much light on the pathway of infection, although it cannot always be definitely traced.

Altmann and Waltner describe 5 cases in which hemolytic streptococci were the cause of tympanogenic labyrinthitis. In each case death was caused by labyrinthogenic meningitis. In 1 case the labyrinthitis followed acute otitis media; in 3 cases, an acute exacerbation of chronic otitis media, and in 1 case, chronic otitis media with cholesteatoma. From a study of the clinical course and the histologic examinations, the authors analyze the role of the oval and round windows in the genesis of labyrinthine changes. In acute exudative otitis media or in acute exacerbations of uncomplicated middle ear infection, extension of the pathologic process usually occurs through one or both windows. It cannot be definitely stated from the information at hand just which of the two windows is more often the portal of entry or in how many instances the infection penetrates through both windows simultaneously. Because the histologic changes occurring in primary invasion of the windows are identical with the secondary reactive changes following a purulent labyrinthine infection through another portal of entry, clearcut interpretations are often difficult to obtain. The unfavorable conditions of drainage, due to the anatomic structure of the labyrinth, facilitate the development of leptomeningitis. The resistance of the mucosal covering of the window membranes to destruction further impedes drainage to the middle ear.

The character of the underlying infection of the middle ear largely determines the genesis of labyrinthitis. Exudative inflammations, as a rule, spread through the windows; proliferative infections (Pneumococcus type III) and chronic infections complicated with cholesteatoma, through the osseous capsule, particularly the semicircular canals. The character of the labyrinthitis is not determined by the character of middle ear infection. The most important pathway of extension of infection to the meninges is along the channels of the modiolus and the vestibule. In 4 of the 5 cases here reported the infection spread through the modiolus.

Although the question of the pathways of endocranial extension of infection has lost some of its importance since recent chemotherapy has been used with such success, it still deserves attention for the sake of the complications that will undoubtedly persist in spite of chemotherapy.

RYAN, Philadelphia.

PRIMARY SUTURE OF NERVES. R. B. ZACHARY and W. HOLMES, Surg., Gynec. & Obst. **82**:632 (June) 1946.

Zachary and Holmes review cases of primary nerve suture which came under observation at the center for peripheral nerve injuries at the Wingfield-Morris Hospital, Oxford, England, from 1940 to 1944. There were 55 cases of primary nerve suture. The results in these cases are compared with results in cases of early secondary suture. Contrary to the widely accepted view, the proportion of good results is higher for early secondary suture than for primary suture. Sepsis was not the chief adverse factor involved in primary suture. Microscopic examination of the site of primary suture in 16 cases indicated that the chief faults were poor technic, inadequate resection of the damaged nerve ends and excessive postoperative tension. There is a great deal to be gained by approximating the ends of the divided nerve to prevent retraction. When secondary suture is performed in a few weeks, the length of nerve to be resected will probably be short; the suture can be performed with precision and without tension, and the prospects of recovery will be good. If deliberate primary suture has been performed, the patient should be watched carefully. If progress appears unduly slow, further resection and resuture should be considered.

J. A. M. A.

THE MARCUS-GUNN SYNDROME. J. L. WELLS, U. S. Nav. M. Bull. **46**:1275 (Aug.) 1946.

Wells reports a case of the Marcus-Gunn syndrome in a white Marine aged 25 which was discovered incidentally in routine physical examination. The family history was not remarkable. The personal history revealed the presence of ptosis and associated winking of the left eyelid in talking and eating since infancy. Except for the syndrome, the general physical condition was normal. The reflexes, sensory status, pupillary reactions and extraocular movements were normal, as were the corneal reflexes and the facial muscles. There was ptosis of the left eyelid. When the mouth was opened wide and the mandible moved to the right, a pronounced elevation of the left upper eyelid occurred. Movement of the mandible to the left failed to elicit the response. As in the majority of cases reported, the movements of the eyelid occurred on contraction of the ipsilateral external pterygoid muscle.

The general varieties of this syndrome are (1) unilateral ptosis, in which the eyelid is raised (*a*) when the mouth is opened and the mandible is moved to the opposite side, (*b*) when the mouth is opened but not when the mandible is moved laterally and (*c*) when the mandible is moved to the opposite side but not when the mouth is opened; and (2) associated movements of the eyelid and jaw without ptosis. Further bizarre associated movements have been reported.

The etiologic factor is obscure, and treatment save for cosmetic and emotional reasons is not indicated.

BERRY, Philadelphia.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Kenneth J. Tillotson, M.D., *Presiding*

Regular Meeting, March 21, 1946

Effect of Penicillin on the Central Nervous System. Dr. Herbert C. Johnson, Dr. A. Earl Walker, Dr. Theodore J. Case and Dr. Jerry J. Kollros, Chicago.

This paper appeared in full in the Archives (**56**:184 [Aug.] 1946).

DISCUSSION

Dr. Augustus R. Rose, Boston: It is a pleasure for those of us who know Dr. Walker's writings to have him present this fine paper. My experience with the use of penicillin has been confined to investigations on neurosyphilis. As many of you know, there has been considerable pressure for the intrathecal use of penicillin in treatment of neurosyphilis. Prior to the publication of Neyman, referred to by Dr. Walker, which showed the dangers of large doses of penicillin given into the spinal fluid, we at the Boston Psychopathic Hospital gave penicillin to 5 patients by this route. In all cases the dose was less than 10,000 units. In none of these patients was there any evidence of muscular twitchings or convulsions. Fortunately, evidence is accumulating to show that intrathecal administration of penicillin is not necessary in cases of neurosyphilis, although it is indicated in a few cases of purulent meningitis.

I should like to ask Dr. Walker two questions: 1. Has he any idea as to the mechanism whereby the antibiotic substance acts to produce the convulsions? 2. Was the crystalline penicillin used fraction G, K or X?

Dr. William H. Sweet, Birmingham, England: I wish to join in congratulating Dr. Walker on this fine presentation. Having had reports of Dr. Walker's work while it was still in progress, I have watched especially for convulsions in cases of meningitis treated with penicillin. In a group of patients seen when there was only enough penicillin available to give it intrathecally, I saw no convulsive seizures, despite what I felt to be the necessity of giving moderately large doses. A maximum of 20,000 units was given into the cerebrospinal fluid at one time. Some patients with meningitis had the tremors of low amplitude typical of the condition before penicillin was given, and these movements were not exacerbated by the penicillin. Many patients whom I gave intrathecal injections mentioned experiencing a diffuse sensation of warmth at the time. During intracisternal injections of penicillin the warm feeling was likely to be referred to the whole head, whereas during lumbar injections the lower part of the back felt warm.

Recently, at the Massachusetts General Hospital, streptomycin was given to a small child under 1 year of age with meningitis due to Proteus vulgaris. Repeated doses had no convulsant effect, but they were sufficient to clear up the meningitis entirely and leave no sequelae.

I should like to emphasize Dr. Walker's statement that as long as penicillin and streptomycin are used only in doses that are known to be lethal to the organisms usually classified as sensitive to their action no untoward convulsive effects will occur.

Dr. Robert S. Schwab, Boston: I should like to add my word of congratulation on the development and isolation of this material, which appears to be strongly

convulsant in the huge doses used in this study. I saw a patient on Guam with a severe fungous infection of the brain from a shell wound. Penicillin was used intravenously and locally in large amounts. I have no idea of the total amount of penicillin given. After injection he had an acute confusional episode, was disoriented and violent and had a rise in temperature. There was nothing to suggest epilepsy, and there was no focal discharge. This episode lasted twenty-four hours. Local injection of penicillin was discontinued. He improved. Could this delirium be due to the penicillin?

DR. WILLIAM G. LENNOX, Boston: I should like to ask a question along a similar line. In the case of a patient with a low seizure threshold, an epileptic patient for example, is there any evidence that penicillin given intravenously might activate his seizures? I should lke to see an enlargement of the tracings shown on the screen. Some of the convulsions were what clinically would be called myoclonic jerks, and I wonder whether there were any accompanying wave and spike formations in the electroencephalograms. This study has added another substance to the many already known which can cause convulsions. These observations offer an increasing number of leads which, if tracked down, might increase the knowledge of epilepsy. It is interesting that these patients present no pathologic changes.

DR. A. EARL WALKER, Chicago: I am grateful to the discussers for their comments.

We used the penicillin manufactured by ten companies, and we could see no difference in the convulsive effect of the ten products. They all seemed to have essentially the same convulsive effect.

It is quite true that clinically one does not see convulsive manifestations when therapeutic doses are given. One reason is that the amount of penicillin which reaches the cerebral cortex when injected in the lumbar region is only approximately 1 per cent of the dose given. Assuming that 20,000 units was injected, only 200 units gets to the cisterna magna, and 200 units is less than the convulsive threshold dose. The amount over the surface of the brain is still much less than that. We have injected very large amounts of penicillin into the ventricular system, as much as 100,000 units, without producing convulsions. There is, therefore, a great individual variability. I do not know the neural mechanism of the convulsive attacks due to penicillin or the other antibiotic substances.

We did not see the typical wave and spike formations in the electroencephalogram, which, as Dr. Lennox mentioned, are typical of certain types of idiopathic epilepsy. In the majority of the cases the convulsion consisted of a series of spikes, rather than of humps and spikes.

Military Neurology in India with Especial Reference to Deficiency Syndromes in Ex-Prisoners of War. DR. D. DENNY-BROWN.

After comments on the climate and on the composition of armies in India and Burma, the military medical organization was described. Incidental observations confirmed the absence of multiple sclerosis, although diseases such as amyotrophic lateral sclerosis and muscular dystrophy were seen. Meningovascular syphilis was common, but tabes and dementia paralytica were extremely rare. The syndrome of prolapsed intervertebral disk was common among Europeans in India, but scarcely a case was known in Indian nationals. Classic causalgia was a relatively common accompaniment of injuries of the median and popliteal nerves, and there was some evidence that the increased incidence was related to the combined humidity and heat. Cutaneous diphtheria was a problem in jungle warfare, and penetrating jungle head wounds carried a high rate of infection with Bacillus coli. Cysticercosis was seldom seen in the stage of recent invasion, but there was reason to believe that many men were infected. It should be suspected in any soldier in whom epilepsy develops in two to five years after service in India. The hyperpyrexia following heat stroke led to a cerebellar syndrome in some men, and it was considered that hyperpyrexia was the mechanism of the similar ataxia which

was occasionally seen after cerebral malaria. Poliomyelitis was a troublesome problem in 1945, affecting chiefly young men recently arrived in India, even in areas where elaborate precautions against insect transmission had greatly reduced insect-borne diseases. Fecal contamination of water supplies was notorious throughout the East, and it was felt that insistence on decontamination of feces in all known cases of poliomyelitis with more effective disinfectants than the usual "lysol" (saponated solution of cresol U. S. P.) should be made general practice.

Among the prisoners of war released from Rangoon there were, besides cases of "famine edema" and a few residual cases of beriberi, many cases of amblyopia due to retrobulbar neuritis. When severe, this condition was associated with ataxia and deafness. This condition was described in Malaya by Landor and Pallister (*Tr. Roy. Soc. Trop. Med. & Hyg.* **29**:121 [July] 1935) and is certainly a deficiency syndrome. With the release of prisoners of war from Malaya, Batavia, Siam and Indo-China, many more cases of this condition were seen; in addition, a condition of spastic paraplegia resembling lathyrism was observed. The nature of these conditions was discussed and illustrated.

DISCUSSION

DR. HERRMAN L. BLUMGART: Since returning from India, I have wanted to make another visit but did not anticipate as charming and fascinating a "return" as that this evening. As Dr. Denny-Brown says, it is a country of sharp contrasts. It is too rich and too poor, too hot and too cold, too wet and too dry.

The British plan in regard to consultants was far superior to the American. Our outfit had only three consultants—medical, surgical and neuropsychiatric. American forces were deployed in Burma, India and China. During the year, we were traveling a good deal of the time by airplane. The experience we had was dissimilar to Dr. Denny-Brown's in that we saw no vitamin deficiencies except in prisoners of war who came in from China and Burma.

My interest was primarily medical. I saw practically every tropical disease in the textbooks. Amebiasis was the most urgent problem. Of the conditions that might interest you there were several. Cutaneous diphtheria was first to be recognized in Burma. It was chiefly diagnosed as oriental sore and was then suspected to be beriberi. Several patients died of congestive failure, and the disease was recognized. It was one of the very important medical conditions in the Burma campaign. Poliomyelitis was particularly virulent and fatal, with high frequency of the bulbar type and a mortality rate of 40 per cent. Fortunately, the disease was not prevalent. Among the Chinese troops in Burma, cerebral malaria was frequent. Filariasis was difficult to diagnose. We saw approximately 20 cases of smallpox a year, although our men had been vaccinated. We had little cholera, although while I was in Chungking there were 80,000 cases among the civilian population. With proper educational measures and vigilance, the incidence of cholera was reduced to practically nil. Only 20 cases occurred in the last few months, and these were of men who drank some "crystal clear water" near an infected village. With the advances in chemotherapy these diseases have lost their horror. The mortality of cholera has usually varied from 40 to 60 per cent, but with the use of intravenous administration of fluids, transfusions, sulfadiazine and penicillin it can evidently be reduced to 2 per cent.

The climate is just as Dr. Denny-Brown described it, but no one spending a period of time in India can fail to look back on it as an extraordinary personal experience and an even more fascinating professional experience.

DR. ROBERT S. SCHWAB: The part of Dr. Denny-Brown's talk which impressed me most was that which revealed the patience and skill with which he collected all this material. Many of us in the service traveled thousands of miles and had interesting clinical experience, but we did not succeed in keeping accurate notes —we have only vague memories. I am greatly impressed with the completeness of these observations and their value to clinical neurology.

In August and September I had an opportunity, as neurologist in a naval hospital in Guam, to examine 960 evacuees, American and British prisoners of war who had been in prison camps for three years. They had been moved in 1943 and 1944 under atrocious conditions to Japan, near Tokyo. This group represented mostly ambulatory patients sent to the naval hospital to get a week of complete examinations—neurologic, psychiatric and electrocardiographic and other laboratory studies. The results of these examinations are in line with what Dr. Denny-Brown has presented. My colleagues and I saw for the first time—and it was rather new to our ophthalmologist—patients with retrobulbar neuritis. Ten per cent of these patients showed varying degrees of visual loss with central scotoma and atrophy around the macula. We wondered whether they would regain the vision that they lost during the period in which they were on a deficient diet. They were given an adequate diet with the addition of large amounts of vitamin B complex. Some of the losses of weight were amazing to me—from 75 to 80 pounds (34 to 36.3 Kg.) in men from Corregidor—but the patients gained back from 5 to 10 pounds (2.3 to 4.5 Kg.) a week. Thirty per cent of these men gave a history of beriberi on the interview questionnaire, but I think that two thirds of these men had nutritional edema instead. There were some ataxia and peripheral neuritis with residual loss of reflexes. Many complained of painful feet. I saw some cases of paraplegia with spastic reflexes. The patients had been bedridden for long periods and had not received any form of medical treatment. We obtained electrocardiograms on the men; not many were abnormal. All the patients were reasonably young men, who should not have had any cardiac disease at their age.

I shall mention one form of treatment that I learned of, particularly among the Canadians from Hongkong and our men from the Chinese prison camps. The patients were bedridden and could not work. The Japanese doctors would make a diagnosis of "wet beriberi" and then use the gunpowder treatment. A pile of gunpowder 2 cm. high was ignited over points along the distribution of the peripheral nerve; the burn caused an indurated ulcer, which persisted several months. It was thought at first that this was a form of torture, but it was done in so many different camps in cases of peripheral neuritis that I wonder what the explanation really was.

I talked with some of the doctors who were with these men, and they told me the Japanese had vitamin compounds for sale. On hospital ships they were able to make assays of these vitamin compounds, which were found to be inert. The products were commercial preparations on sale throughout Japan. From this group of patients we obtained the information that the spring of 1942 was the worst with respect to neurologic disease and symptoms. The diet was extremely poor; but it improved in 1944, and an effort was made to prevent nutritional disease. In 1945 the diet was somewhat improved, so that deficiency diseases would not interfere too much with the use of the men as workers. Many worked north of Tokyo in coal, zinc and lead mines for fifteen hours a day. When one saw these men, 50, 60 or 70 pounds (22.7, 27.2 and 31.8 Kg.) underweight, one wondered how they could have worked under such conditions, with painful and swollen feet. I saw only 2 men out of 960 whom I thought had a neurosis. The medical officers whom I talked with, who were also prisoners, said that the psychopathic and neurotic prisoners had died of cold, heat, starvation and beatings in the struggle for survival of the fittest. The men with unstable personalities among the prisoners died first, so that the percentage of neuroses among the men who came back was small. The Japanese were afraid of psychotic prisoners; often violent ones were allowed to escape, and some were shot when they tried to come back. The officers who were prisoners of war had an easier time in that they were excused from hard labor. Their great trouble was idleness. The hobbies that they developed would make an interesting paper in itself.

I think this society is fortunate to have heard this interesting paper.

DR. D. DENNY-BROWN: With respect to the prognosis of nutritional retrobulbar neuritis, I can say that with intramuscular injections of liver extract the

patients with the mild form recovered in four to six weeks. The patients with vision reduced to 50/100 might recover near-normal vision; those with a reduction to 80/100 usually recovered only 50/100 vision. The severer types might be expected to leave residual structural changes.

Beriberi is a recoverable disease. Recovery is slow and steady with treatment, and undoubtedly the condition had been very common. Most of the patients had recovered before I saw them, but the absence of ankle jerks and tenderness might persist for six months after recovery of motor function.

Of the gunpowder treatment I know nothing, except that it is reputed to be an old Chinese treatment. Vitamin pills had been provided at times by the Japanese, and some were certainly potent; but the Japanese also had large stocks that they had failed to issue.

Frank neurosis was uncommon—I do not know why, whether by elimination of the unfit or for some other reason. My colleagues and I had a series of 27 psychotic men who had been through the period in the Changi camp and had had excellent care.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

Thomas J. Heldt, M.D., *President, in the Chair*

Regular Meeting, Eloise, Mich., Dec. 5, 1946

Laurence-Moon-Biedl Syndrome. Dr. Joseph Slutzky, Eloise, Mich.

The case was reported of a Negro aged 40 with polydactyly, retinitis pigmentosa and mental retardation. This unusual syndrome was first described by Laurence and Moon in 1866.

Five Year Results of Shock Treatment: A Follow-Up Study. Dr. Edward N. Hinko and Dr. Louis S. Lipschutz, Detroit.

In attempting a critical evaluation of the shock therapies, including the insulin coma method, the metrazol convulsion method and the electric shock method, 457 treated patients were compared with a control group of 289 patients. In this study the percentages of paroles, relapses, reparoles and paroles at time of the study were utilized. A comparison of the average periods of hospitalization for treated and for untreated patients was made, and the preliminary results of a follow-up study of patients on parole from both the treated and the untreated group was reported.

It was found that a higher number (9 per cent) of remissions may be expected after shock therapy than when remission is permitted to occur spontaneously. The study also revealed that treatment given during the first year of residence in hospital results in the saving of four hundred and twenty-two hospital days per patient, remission permitting parole occurring in one-third the time required for spontaneous remission.

Prefrontal Lobotomy for Severe Conduct Disorder. Dr. Robert M. Jennings, Eloise, Mich.; Dr. Aage Nielsen, Detroit, and Dr. Milton H. Erickson, Eloise, Mich.

PRESENTATION OF CASE (DR. JENNINGS)

The patient, a young woman, had a long history of severe conduct disorder. Her antisocial conduct dated back to the age of 4 and included such problems as kleptomania, pyromania, oral and anal perversions, nomadism and alleged homicidal acts. Both before and after operation, the patient was given electroencephalographic and intensive psychologic study, including the Wechsler-Bellevue test, the Ellis Visual Memory Test, the Rorschach Personality Study and the Murray Thematic Apperception Test. An anterior leukotomy was done on Oct. 29, 1946. It was

concluded, five weeks after operation, that the leukotomy had brought about definite improvement in the patient's behavior pattern and personality. She apparently had lost the intense, impulsive preoperative drives which had resulted in a long history of overt, aggressive, antisocial behavior, and she appeared to be a quiet, emotionally subdued person. Further studies and continued observation on this case were indicated.

OPERATIVE PROCEDURE (DR. NIELSEN)

After preparation with soap, water, alcohol and "mercresin" (amyltricresols and orthohydroxyphenyl mercuric chloride), injection of 1 per cent procaine hydrochloride was carried out over the area of the proposed incisions. One inch (2.5 cm.) incisions were made equidistant from the midline, about 3.5 cm. anterior to a plane through the external acoustic meatuses and about 3 cm. from the midsagittal suture. The incisions were carried down through the subcutaneous tissue and the galea, exposing the coronal suture on each side. The wounds were held open by mastoid retractors. With a circular saw, a button of bone the size of a quarter was removed on each side. The underlying dura was incised and held back with guy sutures. On the right side the pia-arachnoid was then incised and a ventricular needle inserted in the direction of the lesser wing of the sphenoid bone. The needle was then reinserted somewhat farther posteriorly and the middle fossa was entered, thus giving a definite landmark and assurance that the anterior horn of the lateral ventricle had not been entered. With the ventricular needle as a guide, the frontal association fibers were severed by cutting with a blunt instrument downward, medially and laterally. With use of the blunt instrument and fine suction, it was possible to make a complete sweep from side to side and sever practicaly all the white fibers from the frontal lobe to the thalamus.

Care was taken to avoid the cortical gray matter itself, and large vessels, including the anterior cerebral arteries, were watched for and avoided. During the dissection down to the brain a good view was obtained at all times by means of ribbon retractors inserted into the brain itself. The comparatively little bleeding which occurred during the procedure was easily controlled with the coagulating current.

The same procedure was carried out on the left side.

After complete hemostasis, the wounds were closed with interrupted silk sutures, applied first to the dura; then the buttons of bone were reinserted, and interrupted sutures were applied to galea and skin.

After the second stage of the procedure the patient became somewhat disoriented and drowsy, but the strength of the right hand and her capacity for speech were still present. The patient was then returned to the ward, apparently in good condition.

PSYCHODYNAMIC STUDY (DR. ERICKSON)

The psychodynamic aspects of the patient's obsessive-compulsive criminalistic behavior were discussed in terms of the patient's own remarkable, but unorganized, purely intellectual, insight into her conduct. The primary dynamisms were those of profound rejection of the self and strong destructive attitudes toward society.

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following certifications were made at the meeting of the Board in Philadelphia, May 15-17, 1947:

Psychiatry.—By Examination: Solomon Adelman, Northport, N. Y.; Albert H. Argent, Marion, Ind.; Clinton Harry Bagenstose, New York; James Louis Baker, Forth Worth, Texas; Milton Charles Baumann, Sprigfield, Ill.; Eleanor Beamer-Maxwell, Williamsburg, Va.; William Peter Beckman, Columbia, S. C.; John A. Belisle, Eloise, Mich.; H. Craig Bell, Abington, Pa.; Raymond J. Bennett, Tacoma, Wash.; Nathan K. Bernstein, Utica, N. Y.; Siegfried R. Berthelsdorf, New York; Brian Bird, Toronto, Canada; Douglas D. Bond, Cleveland; Louis D. Boshes, Chicago; Chris J. Buscaglia, Ypsilanti, Mich.; Stuart K. Bush, Denver; Dale Corbin Cameron, Washington, D. C.; Joseph Anthony Cammarata, Dixmont, Pa.; Howard R. Campbell, Dayton, Ohio; Dominick J. Carlisi, West Brentwood, N. Y.; Arthur L. Chandler, Los Angeles; Frank E. Coburn, Iowa City; Samuel Cogan, Brooklyn; Max Cohen, Coatesville, Pa.; Arthur T. Colley, Lyons, N. J.; Henry S. Colony, Fort Worth, Texas; C. Archie Crandell, Greystone Park, N. J.; Bernard A. Cruvant, Washington, D. C.; C. Nelson Davis, Philadelphia; Alcinda P. de Aguiar, Bedford, Mass.; Stanley R. Dean, Stamford, Conn.; Samuel Dinenberg, Philadelphia; William C. Douglass, Palo Alto, Calif.; Lester Drubin, Northport, N. Y.; R. Stuart Dyer, Syracuse, N. Y.; Carl M. Epstein, Topeka, Kan.; David J. Fish, Howard, R. I.; Maria F. Fleischl, New York; John M. Flumerfelt, Cleveland; * David Bernard Foster, Topeka, Kan.; Kate Frankenthal, New York; Richard M. Free, Philadelphia; Henry Freund, Rochester, N. Y.; Robert S. Garber, Trenton, N. J.; Sol Weiner Ginsberg, New York; Sarah E. Glass, Worcester, Mass.; James S. Glotfelty, Sheridan, Wyo.; Gerald L. Goodstone, Syracuse, N. Y.; P. Goolker, New York; Thomas L. Greason, Providence, R. I.; Marvin F. Greiber, Muncie, Ind.; Maurice Grossman, Augusta, Ga.; Lloyd William Hatton, Salina, Kan.; John James Head, White Plains, N. Y.; Friedy B. Heisler, Chicago; Louis Herman, Fort Custer, Mich.; Thomas F. Hersey, New Haven, Conn.; Robert T. Hewitt, Fort Worth, Texas; Edward N. Hinko, Eloise, Mich.; Cotter Hirschberg, Denver; Gerhard Hirschfeld, Norwich, Conn.; Clarence S. Hoekstra, Denver; Oscar E. Hubbard, Dallas, Texas; Portia B. Hume, Berkeley, Calif; James B. Hurley, Milwaukee; George W. Jackson, Little Rock, Ark.; Louis Jacobs, Mount Rainier, Md.; Franklin Johnson, Eloise, Mich.; Leopold Jordani, New York; Rudolph Kaldeck, Boston; Julius Arthur Kaplan, Northampton, Mass.; Samuel R. Kesselman, Brooklyn; Isham Kimbell Jr., Fort Custer, Mich.; Harold N. King, Hampton, Va.; Joseph L. Knapp, Weston, W. Va.; Salmon A. Koff, Mendota, Wis.; Louis Koren, Eloise, Mich.; Samuel H. Korman, Brooklyn; Elinor M. Langton, Philadelphia; Ulrich Ledien, Peoria, Ill.; George Leventhal, Los Angeles; Samuel Levin, Philadelphia; Stanley B. Lindley, Willmar, Minn.; Harry H. Lipcon, Portsmouth, Va.; Sam J. Lipkin, Chicago; Samuel D. Lipton, Chicago; LeRoy M. A. Maeder, Philadelphia; Vincent P. Mahoney, Philadelphia; Joseph A. Manno, Central Islip, N. Y.; Thomas A. March, Poughkeepsie, N. Y.; Samuel H. Marder, Boston; Joseph H. Marshall, Sykesville, Md.; * Richard L. Masland, Winston-Salem, N. C.; Frederick Mayer, Louisville, Ky.; Jay Earl McCormick, Chicago; Gladys McDermaid, Brooklyn; Francis McLaughlin, Baltimore; Carl Miller, Kankakee, Ill.; Harry Moscowitz, New York; Raymond Nadell, Brooklyn; Kenneth C. Nickel, Ypsilanti, Mich.; Mervyn M. Nickels,

Traverse City, Mich.; Richard H. Parks, Warren, Pa.; Roy A. Phillips, Hines, Ill.; Edgar Lee Porter, Wayne, Pa.; Florence Powdermaker, Washington, D. C.; George S. Rader, Bloomington, Ind.; * Stephen W. Ranson, Baltimore; Samuel Reznick, Los Angeles; Sol A. Robins, Amityville, N. Y.; Milton H. Rodofsky, Boston; Roland D. Roecker, Millington, N. J.; William R. Rosanoff, Alhambra, Calif.; Morris M. Rosenthal, Chicago; Daniel M. Rosman, Topeka, Kan.; Emanuel Rubin, Canandaigua, N. Y.; Thomas A. Ruddell, Allentown, Pa.; Julius Rudnick, Brooklyn; Benno Safier, Agnew, Calif.; George Saslow, St. Louis; James P. Scanlon, Llanerch, Pa.; Gerhard Schauer, Floral Park, N. Y.; Ber M. Schegloff, Boston; Rosa B. Schub, Trenton, N. J.; Bruno G. Schutkeker, Buffalo; Emmanuel Silver, Palo Alto, Calif.; Jacob Sirkin, Newark, N. Y.; Charles A. Smith, Oklahoma City; Stewart R. Smith, Quincy, Mass.; Bernard S. Stell, Buffalo; Marvin Stern, Brooklyn; H. Gordon Stratton, New Toronto, Ontario, Canada; Theodore P. Suratt, Cleveland; Florence L. Swanson, Seattle; David R. Talbot, Los Angeles; Thomas Thale, St. Louis; Charles W. Tidd, Beverly Hills, Calif.; Oswald V. Todd, Washington, D. C.; Leo Milton Traub, Palo Alto, Calif.; Max Unger, Middletown, N. Y.; Robert J. Van Amberg, East Orange, N. J.; Abraham L. Waldman, Norristown, Pa.; Guy M. Walters, Willard, N. Y.; Benjamin Wassell, Greystone Park, N. J.; Max E. Witte, Portland, Me.; Ralph I. Wolfe, Toronto, Canada; Horatio C. Wood, Peoria, Ill.; Richard V. Worthington, Framingham, Mass.; Donovan G. Wright, Great Lakes, Ill.; Harold S. Wright, New York; Miltiades L. Zaphiropoulos, New York; Ladislaus J. Zbranek, Fort Worth, Texas.

Psychiatry.—On Record: Neil D. Black, Marcy, N. Y.; Frederick M. Cook, Lexington, Ky.; Clarence M. Crawford, Kingston, Ontario, Canada; George E. Charlton, Norfolk, Neb.; Harry Elkins, Augusta, Me.; Earl W. Fuller, Greystone Park, N. J.; Joe Funderberg, Torrance, Pa.; John Herbert Hare, Evansville, Ind.; Anita W. Harper, Harrisburg, Pa.; Sidney Klein, New York; Hyman L. Levin, Buffalo; John Francis McNeil, Beacon, N. Y.; John A. P. Millet, New York; Bryant Edward Moulton, Winchester, Mass.; Ione Pinney, Stockton, Calif.; James P. Sands, Millville, Pa.; Abram J. Spor, Middletown, N. Y.; John F. Stouffer, Philadelphia; Louis F. Verdel, Northport, N. Y.; Ray L. Whitney, Waverley, Mass.; George W. Wilson, Chicago.

Neurology.—By Examination: Kenneth Harvey Abbott, Columbus, Ohio; Pearce Bailey, Washington, D. C.; Ruth I. Barnard, Topeka, Kan.; * Samuel Cohen, Philadelphia; Justin L. Greene, New York; * Benjamin H. Kagwa, Chicago; * Jacob Lerman, Brooklyn; * Robert L. Meller, Minneapolis; J. Peter Murphy, Washington, D. C.; Hugh Page Newbill, Staunton, Va.; * Leon L. Rackow, Tuscaloosa, Ala.; Edward P. Roemer, Madison, Wis.; Jack George Sheps, Orangeburg, N. Y.; * Stephen C. Sitter, Washington, D. C.; Eli L. Tigay, Chicago.

Neurology.—On Record: Charles S. Kubick, Boston; Milton K. Meyers, Philadelphia; Ignatius N. W. Olninck, New York.

Neurology and Psychiatry.—By Examination: Helen Blake Carlson, Chicago; Elic A. Denbo, Camden, N. J.; Edward Gendel, New York; Major Albert J. Glass, M.C., A. U. S., Augusta, Ga.; Bernard Goodman, Miami Beach, Fla.; Harrington V. Ingham, Los Angeles; Samuel S. Kaufman, New York; Albert E. Rauh, Lyons, N. J.; Harry A. Teitelbaum, Topeka, Kan.

Neurology and Psychiatry.—On Record: George E. Price, Seattle.

* Denotes complementary certification.

CERTIFICATIONS TO AMERICAN BOARD OF NEUROLOGICAL SURGERY

At its meeting in Chicago, June 3 to 5, 1947, the American Board of Neurological Surgery issued its certificate to the following candidates*: Frank M. Anderson, Los Angeles; Robert B. Bassett, St. Louis (May 1, 1947); Leon L. Bernstein, Topeka, Kan.; Howard A. Black, Sacramento, Calif.; August Buermann, South Orange, N. J.; James B. Campbell, Boston; Herbert G. Crockett, Los Angeles; Henry M. Cuneo, Los Angeles; Edward W. Davis, San Francisco; Arthur R. Elvidge, Montreal, Canada; Abraham Ettleson, Los Angeles; Emanuel H. Feiring, New York; Arthur I. Finlayson, Omaha; John D. French, Rochester, N. Y.; O. Hugh Fulcher, Washington, D. C.; Hugh W. Garol, San Jose, Calif. (Sept. 1, 1947); J. Worden Kane, Binghamton, N. Y.; Erich G. Kreuger, New York; Vasilios S. Lambros, Washington, D. C.; Peter Lehmann, Vancouver, British Columbia, Canada; Edgar S. Lotspeich, Cincinnati; Collin S. MacCarty, Rochester, Minn.; Hunter J. Mackay, Seattle; Juan de Dios Martinez-Galindo, Charlottesville, Va. (May 1, 1947); Harry P. Maxwell, Milwaukee (Oct. 1, 1947); W. B. Patton, Birmingham, Ala.; Raymond H. Quade, Neenah, Wis.; Robert Raskind, Memphis, Tenn.; Henry A. Shenkin, Philadelphia; Alfred Uihlein, Rochester, Minn.; Philip J. Vogel, Los Angeles; Exum B. Walker, Atlanta, Ga.; Willard B. Weary, Dallas, Texas; Arthur A. Wilson, Charleston, W. Va.; Jack I. Woolf, Dallas, Texas.

*The date of certification, unless otherwise indicated in parentheses, was June 1947.

POLIOMYELITIS CONFERENCE, WARM SPRINGS, GEORGIA

A three day clinical conference on the diagnosis and treatment of poliomyelitis will be held at Warm Springs, Ga., on September 15, 16 and 17, the twentieth anniversary of the founding of Georgia Warm Springs.

The clinical conference will be led by approximately twenty of the nation's authorities in the fields of neurology, pathology, pediatrics, orthopedics, physical medicine and internal medicine, who will present papers reviewing the advances in knowledge of poliomyelitis in these fields.

The papers and discussions will constitute a new book on diagnosis and treatment of the disease, for publication in 1948. Clinical demonstrations of modern treatment methods will be given by the medical staff of the Georgia Warm Springs Foundation.

Physicians interested in attending this conference should address inquiries to the Georgia Warm Springs Foundation, 120 Broadway, New York 5. A complete program of the meeting will be available on request.

AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

At the seventy-first annual meeting of the American Association on Mental Deficiency, held in St. Paul, May 27 to 31, the following officers were elected: president, Dr. Lloyd Yepson, Trenton, N. J.; president elect, Dr. Edward J. Humphreys, Columbus, Ohio; secretary-treasurer, Dr. Neil A. Dayton, Mansfield Depot, Conn.; editor of journal, Dr. Edward J. Humphreys.

Final plans were outlined for the First International Congress on Mental Deficiency, which will be held in Boston, at the Hotel Statler, May 11 to 15, 1948. This meeting is to commemorate the first American institution for mentally defective persons, established in Boston in 1848. It is anticipated that there will be delegates and speakers from North and South America, the British Isles, Europe, Australia and New Zealand. The chairman for the committee on arrangements is Dr. C. Stanley Raymond, Wrentham, Mass.

Obituaries

EDWARD BOYNTON ANGELL, M.D.

1856-1947

Dr. Edward Boynton Angell, for many years active in neurology in central New York state, was born on Oct. 30, 1856, at McLean, N. Y., the son of Edward and Austana (Boynton) Angell. He received his preliminary education in the public schools of Binghamton, N. Y., and the Waverly High School. In 1877 he was graduated from the University of Rochester with the degree of Bachelor of Arts and entered the University of Pennsylvania School of Medicine, from which he received his medical degree in 1881.

After his graduation he served an internship in St. Mary's Hospital, Philadelphia, and in the Philadelphia Infirmary for Nervous Diseases from 1882 to 1883, where he worked closely with Dr. Weir Mitchell. Leaving Philadelphia in 1883, Dr. Angell opened an office in Rochester, N. Y., where he practiced as a neurologist until his retirement in 1933.

Dr. Angell was one of the founders of the Rochester Academy of Medicine and for a while served as president of that organization. In 1903 he was elected vice president of the Medical Society of the State of New York. He also served a term as president of the Medical Society of Central New York. In 1891 Dr. Angell was elected to the American Neurological Association and served as vice president in 1907. After his retirement he went to live in Cold Spring, N. Y., where he could indulge in his great hobby of trout fishing. On April 23, 1947 Dr. Angell died rather suddenly, of a cerebral hemorrhage. He is survived by a son and three grandchildren.

To those of us who remember Dr. Angell at his regular attendance at the meetings of the American Neurological Association, he was a soft-spoken, kindly gentleman of the old school. Formerly we saw him regularly at the annual meetings, but of recent years, as his health failed, we saw less of him.

Book Reviews

Penicillin in Neurology. By A. Earl Walker, M.D., Associate Professor of Neurological Surgery, the University of Chicago, and Herbert C. Johnson, M.D., Resident Neurological Surgeon, the University of Chicago. Price $5. Pp. 202, with 26 tables and 95 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

By presenting the results of their animal and human experimental work on penicillin and integrating their material with the many reports flooding the periodicals in this active and fruitful field, the authors have produced a most useful monograph for all who would utilize penicillin therapy understandingly.

After briefly discussing antibiotics and factors influencing their effective action, the authors present their technic for culturing the offending organism and determining its sensitivity to penicillin, stressing the necessity of this knowledge for proper management. Then are described the experiments which demonstrate the failure of penicillin systemically administered to penetrate the hematoencephalic barrier in the normal brain, while proving its passage in the presence of meningitis. The spinal fluid levels attainable with systemic administration are measured and compared with the concentration needed for therapeutic effect. Since the attainable levels frequently do not suffice, the complemental use of intrathecal, intracisternal and intraventricular injections, and the indications and dangers thereof, are described. The rationale of these procedures is worked out by studying the dispersion of various concentrations of penicillin throughout the cerebrospinal fluid system and correlating the concentrations with clinicopathologic effects. Employing bioassay and electroencephalographic and neuropathologic studies the authors have been able to show that effective concentrations of penicillin can be safely applied to the brain, but stress that intracisternal and intraventricular injections may be required to put the penicillin where it is needed because intrathecal lumbar injection does not disperse well enough. The convulsant effects of overdosage are demonstrated clinicopathologically and by electroencephalogram.

As surgeons, the authors are keenly alert to the possibility of a loculated, poorly draining abscess being the cause of relapse in pneumococcic meningitis, and urge radical simultaneous therapeutic and diagnostic measures, including ventriculography, to discover any suspected focus, which can then be drained surgically. They recognize the amazing control of neurosurgical infections that penicillin has brought, but emphasize the truism that penicillin therapy is never a substitute for adequate surgical drainage. An original technic using penicillin intrathecally in the management of spina bifida is described. The indications for supplementing penicillin with sulfonamide drugs are adequately noted.

In discussing the role of penicillin in neurosyphilis, the authors cite the literature and, while recognizing the efficiency of penicillin, recommended a combination of penicillin therapy and other standard treatment technics. Experience at Bellevue Hospital indicates that adequate penicillin therapy alone suffices, because of the dramatic and sustained return to inactivity of the spinal fluid (Dattner-Thomas). Elsewhere results in treatment of dementia paralytica and tabes have been better when penicillin is combined with malaria. However, the risk is greater.

Finally, Dr. Walker and Dr. Johnson briefly evaluate the neurotoxicity of streptomycin, streptothricin, actinomycin and clavacin and conclude that only streptomycin is safe to employ effectively, the others causing severe damage to the brain, convulsions and death in therapeutic concentrations. As of May 1946, few reports of the efficiency of streptomycin were available, but early hopes are being borne out that a potent weapon against influenza, Salmonella and Escherichia coli infections, and possibly tuberculosis meningitis, is now available.

The authors, both Army neurosurgeons, have done the internist, the neurologist and the neurosurgeon a service in presenting this practical monograph.